Covalent Adducts from 2-Substituted 5-Arylazotropones and Nucleophiles and their Fate

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Working in $(CD_3)_2SO$/MeOH 98:2, 2-methoxy-5-[(4-methylphenyl)azo]-2,4,6-cycloheptatrien-1-one (**1a**) was found to add either MeO^-, giving the stable *gem*-dimethoxy σ-adduct **2a**, or EtS^-, to give initially to the C-2 σ-adduct **4a;** on neutralization, the latter gave *ipso* (C-2) replacement of OMe by SEt, while the former returned to the starting material, *via* the neutral σ-adduct **3a.** In contrast, in the same medium, 2-ethylthio-5-[(4-methylphenyl)azo]-2,4,6-cycloheptatrien-1-one (**5a**) was found to add EtS^- at both C-2 and C-7; on neutralization products of both *ipso* substitution (**5a**) and *ipso*- plus tele-substitution (C-7) (**8**) were isolated.

Introduction

Tropone derivatives are prone to nucleophilic addition to give σ-adducts [1], including elaborated ones from polycyclic troponoids like colchicine [2], in competition with electron transfer yielding radical anions [3]. Substituents that, like methoxy, have electron-releasing effect, deactivate the troponoid ring toward attack by nucleophiles [1]; by contrast, electron-attracting substituents, like Cl or SR, activate the ring toward formation of σ-adducts by nucleophilic attack at C-2 [5] or C-7 [6], as directly established by NMR spectroscopy, or at other ring positions, as inferred from UV spectra [3, 4].

Negative-charge acceptance is the main driving force dictating the position of attack by the nucleophile at the troponoid ring, as illustrated by the comparison of alkylthiolate attack at C-7 in 2-ethylthiotropone [7] or C-2 in 2-alkylthio-5-nitrotropone, where C-7 attack would not benefit from charge acceptance by the nitro group [8].

We have extended these studies to the azo group as a potentially activating [9] and modifiable group. New interesting facets about the interaction of these systems with nuclephiles have emerged and are reported here.

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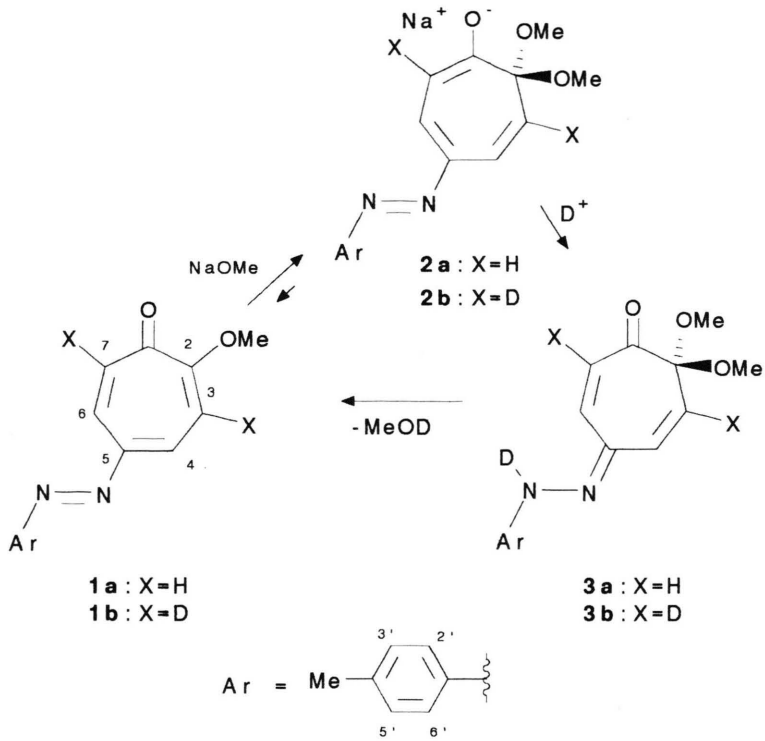
Results and Discussion

On addition of NaOMe, in slight molar excess, to a yellow-orange 0.01–0.05 M solution of 2-methoxy-5-[(4-methylphenyl)azo]-2,4,6-cycloheptatrien-1-one (**1a**) [10] in dried $(CD_3)_2SO$–CD_3OD 98:2 at room temperature, the UV absorption at λ_{max} 387 nm due to **1a** immediately disappeared, the color turning to deep red (λ_{max} 506 nm) that persisted for weeks. On neutralization the color turned immediately to bright orange-yellow (λ_{max} 430 nm), but faded gradually, the original color of **1a** being fully restored in 3–4 h. On parallel ^1H NMR examination, the UV absorptions at λ_{max} 506 and 430 nm could be attributed to species **2a** and **3a,** respectively (Schema 1). All protons of **2a** and **3a** were assigned as shown in the Table, based also on parallel examination of the deuterated substrate **1b,** which generated **2b** and **3b.** We could distinguish between H-4 and H-6 for **2a** from COSY spectra. It should be noticed that protons in the adducts at ring positions to which the negative charge can be delocalized have undergone an upfield shift (Table). This is especially marked for **2a** and extends to the benzenoid ring, testifying of the involvement of the arylazo moiety in the activation. An unusual behaviour of this system was discovered following neutralization, by which a relatively stable neutral intermediate **3a** was formed; this can be attributed to efficient negative-charge acceptance by the arylazo moiety.

With ethylthiolate as nucleophile the situation proved to be more complex. With slight molar ex-



Scheme 1

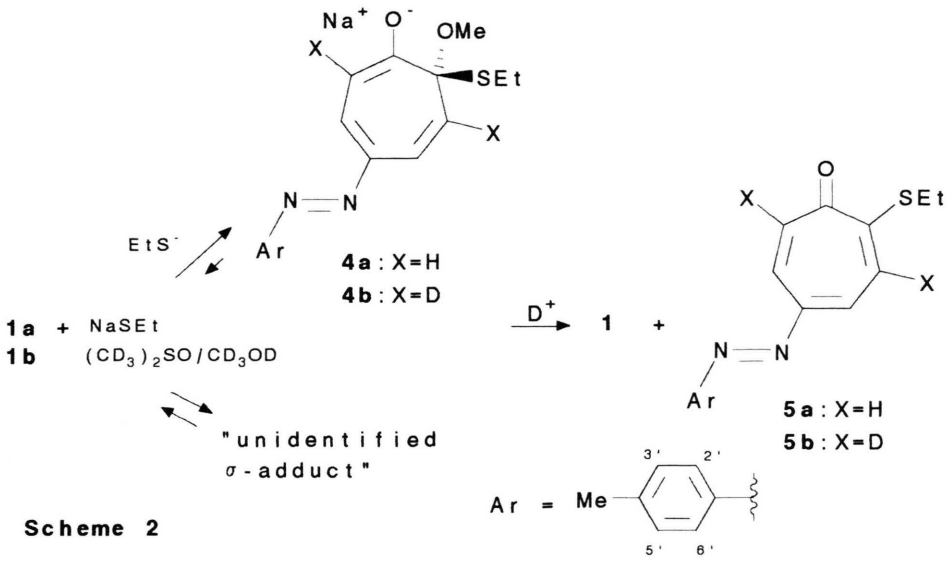
Table I. ^{1}H NMR data[a] for several troponoids and their σ-adducts.

Proton (s) at C atom	**1a**	**2a**	**3a**	**4a**	"unidentified σ-adduct"	**6**
MeO-2	3.99 s	4.08 br.s	4.00 s	4.16 br.s	4.16 br.signal[n]	
EtS-2				3.15 br.signal[i]		[r]
3	7.27 d, 10.4[b]	5.48 d, 10.7[e]	5.90 s, 11.0[g]	5.56 d, 9.4[l]	6.26 d, 11.8[o]	5.90 br.signal
4	7.96, dd, 10.4, 2.2[c]	6.99 d, 10.7[f]	6.91 d, 11.0[h]	6.8–7.0[m]	6.8–7.0[p]	6.7–7.0 br.signal
6	8.05 dd, 12.7, 2.2[d]	7.02 d, 11.1[f]	6.92 d, 12.2[h]	6.8–7.0[m]	6.8–7.0[q]	6.7–7.0 br.signal
7	7.21 d, 12.7[b]	4.96 d, 11.1[e]	5.96, 12.2[g]	5.42 d, 12.0[l]	5.90 d, 13.8[o]	5.25 br.signal
2′(6′)	7.42 d, 8.2	7.09 d, 7.5	7.13 d, 8.2	7.09 d, 7.4	7.09 d, 7.4	7.05 br.signal
3′(5′)	7.82 d, 8.2	7.36 d, 7.5	7.34 d, 8.2	7.35 d, 7.4	7.35 d, 7.4	7.30 br.signal
Me-4′	2.43 s	2.28 s	2.30 s	2.50 s	2.50 s	[r]

[a] In the order δ, multiplicity or broad signal (br.signal), J; [b] absent in **1b**; [c] 7.96 br.d, 2.2 in **1b**; [d] 8.05 br.d, 2.2 in **1b**; [e] absent in **2b**; [f] br.signal in **2b**; [g] absent in **3b**; [h] br.signal in **3b**; [i] CH_2, while the CH_3 signal was submerged; [l] absent in **4b**; [m] br.signal in **4b**; [n] OMe.; [o] absent in "unidentified σ-adduct"; [p] 6.90 (or 7.02) br.signal in "unidentified σ-adduct"; [q] 7.02 (or 6.90) br.signal in deuterated "unidentified σ-adduct"; [r] submerged.

cess of thiolate, immediate formation of σ-adduct **4a** was accompanied by the slower formation of another similar species that could not be identified and was therefore termed "unidentified σ-adduct" (Scheme 2 and Table). On neutralization, both σ-adducts immediately disappeared while **1** re-appeared, accompanied by trace amounts of the C-2 substitution product **5a.** The structural attribution was aided by parallel experiments with the deuterated substrate **1b** (Table).

A practical entry to **5a** was provided with a better leaving group, Cl, in place of OMe, and with



Scheme 2

$(CH_3)_2SO$ as solvent and an equimolar amount of EtSNa (Experimental) [11]. Reaction of **5a** with ethanethiolate led immediately to the *gem*-diethylthio σ-adduct **6,** which is characterized by broad ^1H NMR signals, including those for the aryl system. This can be explained by admitting the presence of complex **7** in tiny amounts in rapid, on the NMR time scale, equilibrium with **5a** and **6.** This is also supported by the results of neutralization of the reaction mixture, by which the formation of **5a** was accompanied by comparable amounts of the disubstitution product **8.** Surprising as the oxidative substitution at C-7 to give **8** may be, there are precedents in troponoid chemistry of formal hydride replacements by amine nucleophiles [12].

Formation of mainly **6** on treatment of **5a** with ethanethiolate does not contradict our initial assertion that electron-accepting groups like RS activate the troponoidal ring to nucleophilic attack. The case in Scheme 3 recalls that of 2-methylthio-5-nitrotropone with methanethiolate, where only C-2 addition was observed [8]. Clearly, both the nitro and the azo group favor attack at C-2 by charge dispersal on the activating group, which can not occur on attack at C-7. However, the azo group allows a 2-alkylthio substituent to perform transannular (C-7) activation (Scheme 3). The azo group also possesses the potential advantage, over the nitro group, of easy manipulation that may make this system synthetically useful.

Experimental

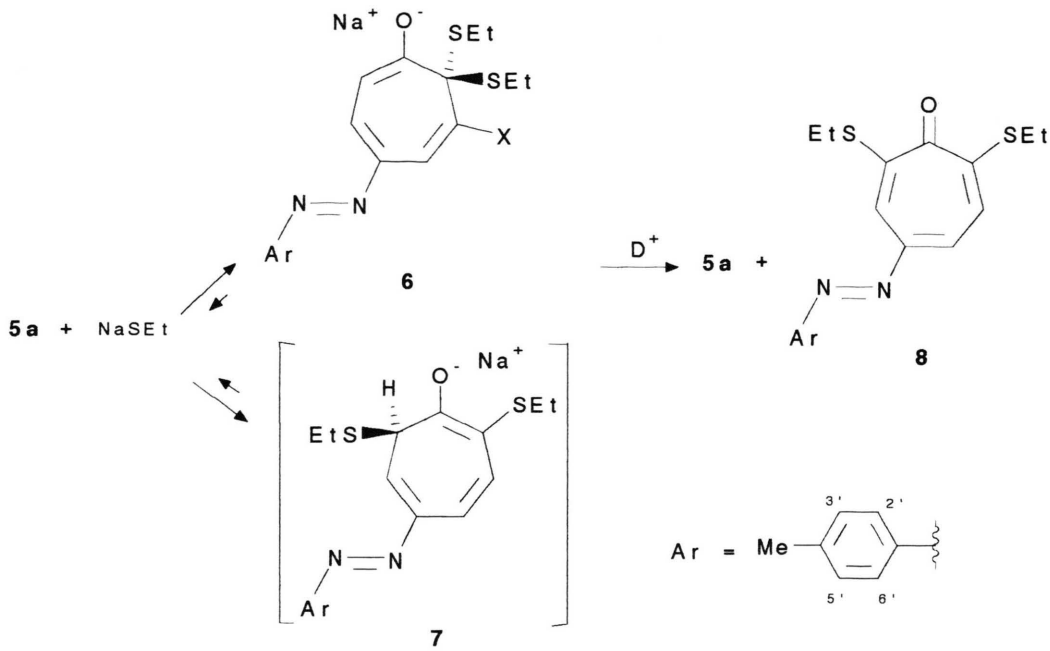
General. – All evaporations were carried out *in vacuo*. TLC was performed on Merck Kieselgel $60PF_{254}$, 2 mm thick plates, UV spectra were obtained using a Perkin-Elmer Hitachi 200 spectrophotometer. NMR spectra were taken on a Varian Gemini 200 spectrometer (199.975 MHz for ^1H); δ values are reported with respect to internal TMS (= 0 ppm) and J values in Hz; $^1H-^1H$ COSY [13]. Mass spectra (EI) were taken with a Kratos MS80 spectrometer with home-built computerized acquisition system

Materials. – $(CD_3)_2SO$ (C. Erba 99.5% ^2H) was distilled from CaH_2 under dry Ar and stored over activated 3 Å molecular sieves. CD_3OD (C. Erba 99.5% ^2H) was used as such.

2-Hydroxy-5-[(4-methylphenyl)azo]-2,4,6-cycloheptatrien-1-one [14] and [3,5,7-$^2H_3$]-2-hydroxy-2,4,6-cycloheptatrien-1-one [15] were prepared according to known procedures.

Synthesis of 2-Methoxy-5-[(4-methylphenyl)azo]-2,4,6-cycloheptatrien-1-one (**1a**)

2-Hydroxy-2,4,6-cycloheptatrien-1-one (0,20 g, 0,83 mmol) was suspended in Et_2O (15 ml) and treated with excess of a solution of diazomethane in Et_2O. After 2 h the mixture was evaporated and the residue was recrystallized from acetone obtaining **1a** [10] as orange-red needles in quantitative yield, m.p. 196–197 °C (lit. [10]; λ_{max}/nm (log ε) (EtOH) 382 (4.4); *m/z* 254 (40%, $M^{+\cdot}$), 226 (1, M–CO), 135 (11, M–ArN_2), 119 (16, M –



Scheme 3

troponoid moiety), 91 (100); hrms *m/z* 254.10586 ± 0.00150 ($C_{15}H_{14}N_2O_2$ requires 254.10552).

Synthesis of [3,7-$^2H_2$]-2-Methoxy-5-[(4-methylphenyl)azo]-2,4,6-cycloheptatrien-1-one (**1b**)

Prepared from [3,5,7-$^2H_3$]-2-hydroxy-2,4,6-cycloheptatrien-1-one *via* [3,7-$^2H_2$]-2-hydroxy-[(4-methylphenyl)azo]-2,4,6-cycloheptatrien-1-one by the methodology used above for **1a.**

Synthesis of 2-Chloro-5-[(4-methylphenyl)azo]-2,4,6-cycloheptatrien-1-one

A solution of 2-hydroxy-[(4-methylphenyl)azo]-2,4,6-cycloheptatrien-1-one (0.051 g, 0.21 mmol) in C_6H_6 (10 ml) was treated with $SOCl_2$ (0.2 ml) under Ar with stirring and the mixture was heated at reflux for 1.5 h. The solvent was evaporated and the residue was subjected to TLC with 8:2 C_6H_6–EtOH; the R_f 0.79 band gave the desired compound as a red solid (0.039 g, 72%), m.p. 164–165 °C; λ_{max}/nm (log ε) (EtOH) 380 (4.1); δ_H ($(CD_3)_2SO$) 8.28 (d, $J_{3,4}$ 10,1, 3-H), 7.76 (dd, $J_{4,3}$ 10.1, $J_{4,6}$ 2.0, 4-H), 8.03 (dd, $J_{6,7}$ 12.9, $J_{6,4}$ 2.0, 6-H), 7.35 (d, $J_{7,6}$ 12.9, 7-H), 7.45 (B of AB, J 8.2, 2′-H and 6′-H), 7.85 (A of AB, J 8.2, 3′-H and 5′-H), 2.45 (s, Me-4′); *m/z* 258 (16%, $M^{+\cdot}$), 230 (2, M–CO), 139 (2, M–ArN_2), 119 (22, M – troponoid moiety), 91 (100); hrms *m/z* 258.05639 ± 0.00180 ($C_{14}H_{11}ClN_2O$ requires 258.05599).

Reaction between 2-chloro-5-[(4-methylphenyl)-azo]-2,4,6-cycloheptatrien-1-one and sodium ethanethiolate

a) In Abs. EtOH. A suspension of 2-chloro-5-[(4-methylphenyl)azo]-2,4,6-cycloheptatrien-1-one (0.039 g, 0.15 mmol) in abs. EtOH (5 ml) was treated with slight molar excess of NaSEt from a 2 M solution in abs. EtOH and stirred at r.t. for 4 h. The mixture was filtered and the filtrate was evaporated to give a deep-red semisolid residue that was subjected to TLC with 8:2 Et_2O-pet. ether; the R_f 0.58 band gave **8** (0.010 g, 19%) while the R_f 0.83 band gave 2-ethylthio-7-ethoxy-5-[(4-methylphenyl)azo]-2,4,6-cycloheptatrien-1-one (0.020 g, 41%).

2,7-Diethylthio-5-[(4-methylphenyl)azo]-2,4,6-cycloheptatrien-1-one (**8**)

Deep-red semisolid; λ_{max}/nm (log ε) (EtOH) 464 (4.0), 412 (4.1), 354 (4.2); δ_H ($CDCl_3$) 2.95 (q, J 7.3, CH_2S-2), 1.47 (t, J 7.3, CH_3CH_2S-2), 6.88 (d, $J_{3,4}$ 12.8, 3-H), 7.96 (d, $J_{4,3}$ 12.8, 4-H), 7.30 (s, 6-H),

3.10 (q, *J* 7.3, CH_2S-7), 1.47 (t, *J* 7.3, CH_3CH_2S-7), 7.30 (B of AB, *J* 8.3, 2′-H and 6′-H), 7.82 (A of AB, *J* 8.3, 3′-H and 5′-H), 2.42 (s, Me-4′); *m/z* 344 (1%, $M^{+\cdot}$), 316 (7, M−CO), 315 (31, M−Et), 284 (11, M−EtS), 225 (2, $M-ArN_2$), 119 (9, M − troponoid moiety), 91 (57), 28 (100); hrms *m/z* 315.06276 ± 0.00210 ($C_{16}H_{15}N_2OS_2$ requires 315.06258), 284.09804 ± 0.00180 ($C_{16}H_{16}N_2OS$ requires 284.09833).

2-Ethylthio-7-ethoxytropone-5-[(4-methylphenyl)azo]-2,4,6-cycloheptatrien-1-one

Red plates, m.p. 80–86 °C; λ_{max}/nm (log ε) (EtOH) 402 (3.5), 332 (4.0), 2.42 (4.0); δ_H ($CDCl_3$) 3.08 (q, *J* 7.4, CH_2S-2), 1.40 (t, *J* 7.3, CH_3CH_2S-2), 7.62 (d, $J_{3,4}$ 8.3, 3-H), 7.84 (dd, $J_{4,3}$ 8.3, $J_{4,6}$ 1.4, 4-H), 8.04 (d, $J_{6,4}$ 1.4, 6-H), 4.40 (q, *J* 7.0, CH_2O-7), 1.40 (t, *J* 7.0, CH_3CH_2O-7), 7.32 (B of AB, *J* 8.0, 2′-H and 6′-H), 7.88 (A of AB, *J* 8.0, 3′-H and 5′-H), 2.42 (s, Me-4′); *m/z* 328 (1%, $M^{+\cdot}$), 300 (20, M−CO), 299 (100, M−Et), 209 (1, $M-ArN_2$), 119 (12, M − troponoid moiety), 91 (77); hrms *m/z* 299.08555 ± 0.00150 ($C_{16}H_{15}N_2O_2S$ requires 299.08542).

b) In $(CH_3)_2SO$. A solution of 2-chloro-5-[(4-methylphenyl)azo]-2,4,6-cycloheptatrien-1-one (0.017 g, 0.066 mmol) in $(CH_3)_2SO$ under Ar was treated at r.t. with NaSEt from a 1.7 M solution in abs. MeOH (0.04 ml) at r.t. The mixture was stirred during 20 min, treated with a drop of 37% aq. HCl, and then with water. The mixture was then extracted with $CHCl_3$ (3 × 10 ml), the organic phase was dried over Na_2SO_4 and evaporated. The residue was subjected to TLC 3:2 Et_2O-pet. ether; the R_f 0.55 band gave **5a** (0.010 g, 53%), while the R_f 0.31 band gave **8** in trace amounts.

Compound **5a** [data for **5b,** when differing from **5a,** are reported within square graphs]. – Orange-yellow plates, m.p. 142–145 °C; λ_{max}/nm (log ε) (EtOH) 416 (4.0); δ_H ($(CD_3)_2SO$) 3.05 (q, *J* 7.4, CH_2S-2), 1.46 (t, *J* 7.4, CH_3CH_2S-2), 7.59 (d, $J_{3,4}$ 14.4, 3-H) [absent], 7.86 (dd, $J_{4,3}$ 10.4, $J_{4,6}$ 2.2, 4-H) [br.d, $J_{4,6}$ 2.2], 8.07 (dd, $J_{6,7}$ 12.7 $J_{6,4}$ 2.2, 6-H) [br.d, $J_{6,4}$ 2.2], 7.11 (d, $J_{7,6}$ 12.7, 7-H) [absent], 7.44 (B of AB, *J* 8.3, 2′-H and 6′-H), 7.84 (A of AB, *J* 8.3, 3′-H and 5′-H), 2.44 (s, Me-4′); *m/z* 284 (38%, $M^{+\cdot}$), 256 (3, M−CO), 165 (5, $M-ArN_2$), 119 (18, M − troponoid moiety), 91 (97), 28 (100); hrms *m/z* 284.09927 ± 0.00165 ($C_{16}H_{16}N_2OS$ requires 284.09833).

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[1] F. Pietra, Acc. Chem. Res. **12,** 132 (1979).
[2] M. Cavazza, C. A. Veracini, F. Pietra, J. Chem. Soc., Perk. Trans 2, **1992,** 2201.
[3] C. Festa, L. Nucci, F. Pietra, A. M. Moresco, L. Pardi, S. Santucci, J. Chem. Soc., Perkin Trans. 2, **1976,** 180.
[4] G. Biggi, F. Del Cima, F. Pietra, J. Am. Chem. Soc. **94,** 4700 (1972).
[5] M. Cavazza, C. A. Veracini, G. Morganti, F. Pietra, Tetrahedron Lett. **1978,** 2593.
[6] F. Pietra, J. Chem. Soc., Chem. Commun. **1974,** 544.
[7] C. A. Veracini, F. Pietra, J. Chem. Soc., Chem. Commun. **1974,** 623.
[8] M. Cavazza, C. A. Veracini, G. Morganti, F. Pietra, J. Chem. Soc., Chem. Commun. **1978,** 167.
[9] J. Kavalek, J. Socha, J. Urbanek, M. Vecera, Coll. Czech. Chem. Commun. **36, 1971,** 209.
[10] H. Enzenberg, D. Schaedler, H. Zaschke, Z. Chem. **22,** 59 (1982).
[11] It should be noticed that with 2-chloro-5-[(4-methylphenyl)azo]2,4,6-cycloheptatrien-1-one and equimolar EtSNa in absolute EtOH in place of $(CH_3)_2SO$, 2-ethyl-7-ethoxy-5-[(4-methylphenyl)-azo]-2,4,6-cycloheptatrien-1-one (41%) and **8** (19%) were formed. Structural evidence is in part based on mechanism: since EtS^- is more reactive than EtO^-, it will replace Cl more rapidly, and EtS at C-2 will activate the ring at C-7, thus allowing EtO^- to enter at this position. Should EtO have been present at C-2, it could never had activated the ring for EtS^- to enter at C-7.
[12] B. Ricciarelli, R. Cabrino, F. Del Cima, C. A. Veracini, F. Pietra, J. Chem. Soc. Chem. Commun. **1974,** 723.
[13] A. Bax, R. Freeman, J. Magn. Reson **44,** 542 (1981).
[14] J. W. Cook, J. D. Loudon, D. K. V. Steel, J. Chem. Soc. **1954,** 530.
[15] F. Pietra, M. Giocasta, F. Del Cima, Tetrahedron Lett. 1969, 5097; E. J. Forbes, M. J. Gregory, D. C. Warrell, J. Chem. Soc. (C), **1968,** 1969.