Selectivity in NBS Bromination. I. The Reaction of Methyl Enol Ethers of Cyclohexane-1,3-diones. A Reexamination

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The n.m.r. spectral analysis utilising solvent- and $Eu(DPM)_3$-induced chemical shifts demonstrates that the reaction of *N*-bromosuccinimide with the methyl enol ethers of cyclohexane-1,3-dione and dimedone leads to bromine substitution at the carbon atom allylic to the olefinic bond, and not at the olefinic site or α to carbonyl, respectively, as previously claimed.

Par l'utilisation en r.m.n. des déplacements chimiques induits par les solvants et $Eu(DPM)_3$, il est prouvé que la réaction entre le *N*-bromosuccinimide et l'éther méthyl énolique de la cyclohexanedione-1,3 conduit à une substitution par le brome sur le carbone allylique à la double liaison, et non pas sur le site oléfinique ou en α du carbonyle, comme cela avait été respectivement annoncé.

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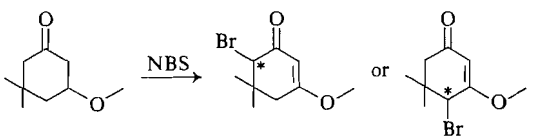
The remarkable antibacterial activity of tetracyclines has been imputed to their characteristic A-ring (1), whose salient chemical features are represented by cyclohexane-1,3-diones bearing carbamoyl and dimethylamino substituents at the 2- and 4-positions, respectively. One of the general approaches to synthesis of model compounds for study of structure–activity relationships and stability factors involves derivatization of 1,3-diones; carbamoylation at the 2-position of 1,3-diones, unsubstituted at that site, can readily be achieved (1, 2), but functionalization of the 4-position is not so easily accomplished.

Bromination of cyclohexane-1,3-dione, dimedone, and monoenolates of 5-phenylcyclohexane-1,3-diones using *N*-bromosuccinimide (NBS) under radical-promoting conditions leads to substitution at the 2-position (3). It has been reported, however (4), that the methyl enol ether of dimedone, 3-methoxy-5,5-dimethylcyclohex-2-enone (**1**), undergoes substitution at the 6-position upon reaction with NBS under similar conditions. In the case of the enolates of symmetrical cyclohexane-1,3-diones, the question of whether substitution occurs at the 4- or 6-position, although a matter of some fundamental significance,[2] does not jeopardize the potential



1 **2** **3**

of the synthetic plan, since hydrolysis of both 4- and 6-bromoenolates would lead to 4-bromo-1,3-dione; but the answer may be of crucial importance to the application of any synthetic scheme which involves this bromination step in the derivatization of *unsymmetrical* cyclohexane-1,3-diones. Arakawa (4) has based his conclusion that **2** rather than **3** is the product of NBS reaction with **1** on what appears to be rather tenuous *chemical* evidence: easy condensation of the bromination product with nitrogen bases and ready reaction with Brady's reagent were thought to be indicative of an α-haloketone, as was formation of an "osazone"[3] rather than a tris(2,4-dinitrophenylhydrazone) upon treatment of the initially formed bromohydrazone[3]

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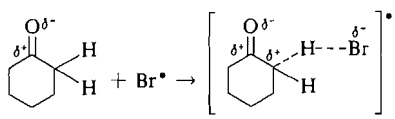
[2]The bromine atom, which is the chain-carrying species in NBS allylic bromination is a strong acceptor radical (5). The passivity of cyclohexanone towards NBS in the presence of cyclohexene is imputed to polar factors affecting the stability of the transition state for hydrogen abstraction: the carbonyl dipole militates against the development of positive charge at the α carbon.



While the same rationale can be expected to apply to the case of simple α,β-unsaturated ketones, the effect of polar substituent groups on the selectivity of bromine substitution in such systems cannot be readily surmised.

[3]The detailed structures of the "osazone" and bromohydrazone were not elucidated.

with an excess of Brady's reagent. Arakawa's decision seemed unjustified, since the relative reactivity of α'- and γ-brominated α,β-unsaturated ketones was not considered, and since it has been established unequivocally by n.m.r. spectral analysis (6) that NBS bromination of cyclopent-2-enone leads to substitution at the 4-position.[4] Also, the claim by Arakawa and Irie (3) that monoenolates of cyclohexane-1,3-dione yield 2-bromo derivatives upon reaction with NBS appeared enigmatic, in face of the claimed dimedone enol ether result. Because of these apparent inconsistencies, and the possible theoretical and synthetic implications a re-examination of these reactions was undertaken.

The n.m.r. spectral analysis of the product of reaction of NBS with **1** establishes that bromine substitution takes place at carbon atom 4 rather than at carbon atom 6, yielding **3** instead of **2** as previously claimed (4); similar examination of the product of NBS reaction of isophorone confirms, as expected, the conclusion by earlier workers (8) that substitution occurs at the 4-position. The reaction of NBS with the methyl enol ether of cyclohexane-1,3-dione also leads to substitution at the 4-position, rather than at the 2-position as formerly reported (3).

The disposition of bromine in the products of the NBS reaction is clear from a consideration of the solvent-induced chemical shifts (Table 1) observed in the n.m.r. spectrum on passing from dilute solution in carbon tetrachloride to dilute solution in benzene ($\Delta = \delta(CCl_4) - \delta(C_6H_6)$ p.p.m.); the signs and magnitudes of the observed shifts are in accord with the generalization that the signals of protons lying behind a reference plane, perpendicular to the αC—CO—α'C plane through the carbonyl carbon atom, suffer positive shifts whereas those of protons in front of the plane undergo negative shifts and those of protons close to the plane exhibit very small and variable shifts (10). The downfield shifts induced by trifluoroacetic acid (TFA) ($\Delta = \delta(CDCl_3) - \delta(TFA)$ p.p.m.) also support these assignments, on the premise that protonation of carbonyl oxygen predominates.

The structures indicated by the solvent shift observations eminently satisfy the data (Table 2) available from reagent shift studies employing $Eu(DPM)_3$, if one assumes complexation of the shift reagent at the carbonyl oxygen (11).

It seems clear from this work that substitution of the methoxyl group for the C-3 hydrogen of cyclic 2-enone systems[6] does not promote a departure from the general rule that radical bromination by NBS effects substitution at the carbon atom allylic to the olefinic bond.

Experimental

The n.m.r. spectra were recorded on a Varian A-60A spectrometer operated at an ambient probe temperature of 40 ± 2 °C. The i.r. spectra were obtained using a Perkin–Elmer Model 621 spectrophotometer.

Materials

Dimedone, 1,3-cyclohexanedione, and isophorone were obtained commercially. The latter liquid was purified by vacuum distillation. The enol ethers were prepared by methylation of the diones using methanol – sulfuric acid according to the procedure of Arakawa and Irie (3).

General Bromination Procedure

NBS brominations were conducted in the standard manner (12) employing a 100 W, Photoflood No. 2 lamp to maintain reflux of carbon tetrachloride while providing a catalytic radiative source. Irradiation was halted as soon as it was estimated, visually, that the NBS had been consumed. The reaction product was quickly cooled, succinimide filtered off and the filtrate concentrated.

The n.m.r. analysis of the filtrates indicated that better than 95% conversion to product was achieved in all cases.

Bromination products were purified by preparative t.l.c. on silica gel GF_{254} using benzene–ether (9:1). Satisfactory microanalyses were obtained for all products.

4-Bromo-5,5-dimethyl-3-methoxycyclohex-2-enone (3)

Compound **3** had m.p. 87–88° (lit. (4) 90–91°); i.r. ($CHCl_3$) ν 1645 (C=O), 1600 (C=C), 1150 (C—O—C) cm^{-1}.

6-Bromo-5,5-dimethyl-3-methoxycyclohex-2-enone (2)

The product of hydrolysis of **3** (13) was treated with ethereal diazomethane to yield ethers **2** and **3** in a 3:2 ratio. Compound **2** was obtained by preparative t.l.c., as described above, in the form of an oil which resisted attempts at crystallization. Its i.r. spectrum showed characteristic absorption at ν 1650 (C=O), 1600 (C=C), 1150 (C—O—C) cm^{-1}.

4-Bromo-3-methoxycyclohex-2-enone

This compound was obtained as an oil and showed characteristic i.r. absorption at ν 1650 (C=O), 1600 (C=C), 1160 (C—O—C) cm^{-1}.

[4]There is also chemical evidence which supports the direction of substitution of cyclopenten-2-ones (*6a*, 7) as well as for isophorone (8) but Hafner and Goliasch (9) have assigned the wrong structure to the product of NBS bromination of cyclopenten-2-one on the basis of observed chemical transformation.[5]

[5]See commentary in ref. *6a*.

[6]An examination of conformationally labile acyclic enone systems and of the theoretical implications of selective bromination of such systems is in progress.

TABLE 1. The n.m.r. solvent shift data (in p.p.m. downfield from internal TMS)*

Compound		2 H	4 H	6 H	3 OCH_3	3 CH_3	5 H	5 CH_3
5,5-Dimethyl-3-methoxy-cyclohex-2-enone (**1**)	CCl_4	5.25	2.21†	2.07†	3.68			1.04
	$\Delta^{CCl_4}_{C_6H_6}$	−0.07	+0.26	+0.01	+0.59			+0.26
6-Bromo-5,5-dimethyl-3-methoxycyclohex-2-enone (**2**)	CCl_4	5.19	2.58, 2.00 (J_{AB} = 18 Hz)	3.86	3.71			1.20
	$\Delta^{CCl_4}_{C_6H_6}$	−0.01	+0.16, +0.26	−0.10	+0.77			+0.34, +0.39
4-Bromo-5,5-dimethyl-3-methoxycyclohex-2-enone (**3**)	CCl_4	5.28	4.24 ($J_{4,6}$ = 1.5 Hz)	2.47, 2.02 (J_{AB} = 16 Hz)‡	3.76			1.23, 1.20
	$\Delta^{CCl_4}_{C_6H_6}$	+0.08	+0.19	−0.04, 0	+0.76			+0.32, +0.39
3-Methoxy-cyclohex-2-enone	CCl_4	5.23	2.36 (t) ($J_{4,5}$ = 6 Hz)	2.11 (t) ($J_{5,6}$ = 6.5 Hz)	3.68		2.0 (m)	
	$\Delta^{CCl_4}_{C_6H_6}$	−0.08	+0.33	−0.02	+0.53		+0.5	
4-Bromo-3-methoxy-cyclohex-2-enone	CCl_4	5.28	4.62 (t) ($J_{4,5}$ = 3.5 Hz)	2.4 (m)	3.76		2.4 (m)	
	$\Delta^{CCl_4}_{C_6H_6}$	+0.13	+0.48	+0.1	+0.88		+0.8	
6-Bromo-3-methoxy-cyclohex-2-enone	CCl_4	5.26	*ca.* 2.8 (t) ($J_{4,5}$ = 9 Hz)	4.29 (t) ($J_{5,6}$ = 4 Hz)	3.74		2.35 (m)	
	$\Delta^{CCl_4}_{C_6H_6}$	+0.10	+0.5	+0.14	+0.87		+0.7	
3,5,5-Trimethylcyclohex-2-enone	CCl_4	5.73 (m)	2.13	2.05		1.90 (t)		1.01
	$\Delta^{CCl_4}_{C_6H_6}$	−0.12	+0.47	+0.03		+0.41		+0.24
4-Bromo-3,5,5-trimethyl-cyclohex-2-enone	CCl_4	5.76 (m)	4.35 (d) ($J_{2,4}$ = 1.4 Hz)	2.50, 2.07 (J_{AB} = 17 Hz)		2.10 (d) ($J_{2,3}$ = 1.4 Hz)		1.26, 1.15
	$\Delta^{CCl_4}_{C_6H_6}$	+0.06	+0.52	+0.06, +0.09		+0.45		+0.30, +0.41

*d, Doublet; t, triplet; m, multiplet.

†The signal at lower field, due to the protons allylic to the olefinic bond, is of appreciably greater line-width than that of the protons α to carbonyl, presumably because of coupling of C-4 protons with the vinylic proton.

‡The doublet character of the two high-field components of the 6 H AB quartet and the corresponding splitting of the 4H proton signal suggests long-range W-coupling between two quasi-equatorial protons and therefore, a quasi-axial conformation for the bromine substituent. The spectra of the other bromination products are complicated by allylic coupling and do not lend themselves as readily to such detailed analysis.

TABLE 2. The n.m.r. reagent* shift data (in p.p.m. downfield from internal TMS)

Compound		2 H	4 H	6 H	3 OCH_3	3 CH_3	5 H	5 CH_3
5,5-Dimethyl-3-methoxy-cyclohex-2-enone (**1**)	0.18 *M* ($CDCl_3$)	5.37	2.27	2.21	3.70			1.06
	$\Delta^{CDCl_3}_{0.024\ M\ Eu(DPM)_3}$	0.87	0.32	0.97	0.13			0.27
6-Bromo-5,5-dimethyl-3-methoxycyclohex-2-enone (**2**)	0.14 *M* ($CDCl_3$)	5.35	2.63, 2.10 (J_{AB} = 18 Hz)	4.06	3.73			1.20
	$\Delta^{CDCl_3}_{0.023\ M\ Eu(DPM)_3}$	0.52	0.19, 0.27	0.75	0.03			0.18, 0.23
4-Bromo-5,5-dimethyl-3-methoxycyclohex-2-enone (**3**)	0.12 *M* ($CDCl_3$)	5.36	4.30	2.60, 2.13 (J_{AB} = 16 Hz)	3.77			1.25, 1.20
	$\Delta^{CDCl_3}_{0.023\ M\ Eu(DPM)_3}$	1.08	0.35	1.18, 1.32	0.16			0.25, 0.42
3-Methoxycyclohex-2-enone	0.21 *M* ($CDCl_3$)	5.38	2.40 (t) ($J_{4,5}$ = 6 Hz)	2.35 (t) ($J_{5,6}$ = 6.5 Hz)	3.70		*ca.* 2.0 (m)	
	$\Delta^{CDCl_3}_{0.038\ M\ Eu(DPM)_3}$	0.84	0.31	0.93	0.13		0.3	
4-Bromo-3-methoxy-cyclohex-2-enone	0.15 *M* ($CDCl_3$)	5.41	4.70 (t) ($J_{4,5}$ = 3.5 Hz)	2.8 (m)	3.76		*ca.* 2.4 (m)	
	$\Delta^{CDCl_3}_{0.025\ M\ Eu(DPM)_3}$	0.55	0.17	0.4	0.09		0.2	
6-Bromo-3-methoxy-cyclohex-2-enone	0.10 *M* ($CDCl_3$)	5.39	*ca.* 2.7 (t) ($J_{4,5}$ = 9 Hz)	4.42 (t) ($J_{5,6}$ = 4 Hz)	3.73		*ca.* 2.4 (m)	
	$\Delta^{CDCl_3}_{0.015\ M\ Eu(DPM)_3}$	0.61	0.2	0.65	0.10		0.3	
3,5,5-Trimethylcyclohex-2-enone	0.14 *M* ($CDCl_3$)	5.89	2.16	2.18		1.93		1.02
	$\Delta^{CDCl_3}_{0.023\ M\ Eu(DPM)_3}$	1.07	0.40	1.15		0.25		0.34
4-Bromo-3,5,5-trimethyl-cyclohex-2-enone	0.15 *M* ($CDCl_3$)	5.84	4.30 (d) ($J_{2,4}$ = 1.4 Hz)	2.61, 2.14 (J_{AB} = 17 Hz)		2.10 (d) ($J_{2,3}$ = 1.5 Hz)		1.26, 1.15
	$\Delta^{CDCl_3}_{0.027\ M\ Eu(DPM)_3}$	1.03	0.31	1.02, 1.14		0.24		0.25, 0.40

*Eu-Resolve, $Eu(DPM)_3$, (Alpha Inorganics) added to $CDCl_3$ solutions in the amounts indicated. d, Doublet; t, triplet; m, multiplet.

6-Bromo-3-methoxycyclohex-2-enone

A methylene chloride solution of 4-bromo-3-methoxycyclohex-2-enone stored for 3 days in the refrigerator underwent isomerization[7] to produce a 1:1 ratio of 4-bromo and 6-bromo isomers, also separated by preparative t.l.c. The latter isomer showed characteristic i.r. absorption at ν 1650 (C═O), 1590 (C═C), 1155 (C—O—C) cm^{-1}.

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