Stereocontrolled Addition of Some Sulphenyl Halides to Bicyclo[3.2.0]-hept-2-en-6-ones and Modification of the Adducts

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The bicycloheptenones (1) and (2) reacted with the sulphenyl chlorides (13)—(15) in a highly regioselective manner to give the corresponding adducts (3)—(8) in 77—92% yield. *m*-Chloroperoxybenzoic acid oxidation of the ketone (5) led to products (9), (10), (22), and (23) resulting from oxidation at sulphur and/or Bayer–Villiger ring expansion. The corresponding dichloroketone (8) suffers oxidation at sulphur only to give the sulphoxide (11) and the sulphone (12). The 7,7-dichlorobicyclohepten-6-one (8) yielded tetra-substituted cyclopentane derivatives (18)—(21) of defined stereochemistry on addition of methanol or piperidine across the C^6–C^7 bond.

AIMING at the stereocontrolled synthesis of cyclopentane derivatives, we wished to prepare arylthiocyclopentanes possessing such additional functionality to allow facile conversion into thioprostanoids. We have shown previously that bicyclo[3.2.0]hept-2-en-6-ones are useful intermediates for the preparation of substituted cyclopentanes since the cyclobutanone moiety can be modified in a number of ways and also guides reactions at the adjacent alkene unit with high stereoselectivity.[1]

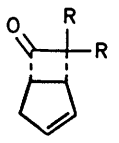
Arylsulphenyl halides had been shown to add to alkenes readily: a large body of evidence suggests that sulphenium ions are intermediates in this process.[2] Thus, our synthetic strategy required addition of arylsulphenyl chlorides to bicyclo[3.2.0]hept-2-en-6-ones followed by suitable modification of the cyclobutanone ring system.

RESULTS AND DISCUSSION

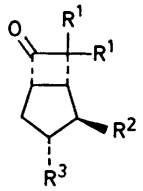
The ketones (1) and (2) reacted with the sulphenyl chlorides (13)—(15) to give the corresponding adducts (3)—(8) cleanly and in high yield. The stereochemistry of the addition products was established by ^{1}H n.m.r. spectroscopy: the signal due to >CH–S– appeared as a slightly broadened singlet ($J \leqslant 2$ Hz) indicating an orthogonal disposition to vicinal protons.[3]

The very high selectivity of the addition reaction is undoubtedly due to the preferential formation of the *exo*-epi-sulphenium ion followed by nucleophilic attack by chloride ion at the less hindered C-3 site (Figure). Reaction of the bicycloheptenol (16) with the sulphenyl chloride (15) gave the halogeno-alcohol (17); the product resulting from intramolecular capture of the intermediate sulphenium ion by the pendant hydroxy-group was not observed.

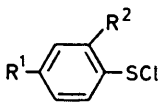
The four-membered ring in the trihalogenobicycloheptanones (7) and (8) was readily cleaved by nucleophiles to give tetra-substituted cyclopentanes of defined stereochemistry.[4] For example, the ketone (8) gave the ester (18) in high yield on treatment with methanol containing ammonium chloride and iron. This reagent cleaved the C^6–C^7 bond in the ketone (8) rapidly under very mild conditions. In contrast, iron or ammonium chloride alone, as well as iron(II) and iron(III) chloride in methanol were ineffective. The ketone (8) furnished the amide (19) on treatment with piperidine. Reaction of the ketone (8) with sodium methoxide in methanol gave the ester (20); under the same reaction conditions the ketone (7) afforded the ester (21). Base-catalysed epimerization of the ester (18) to the thermodynamically



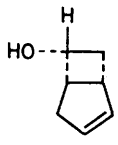
(1) R = H
(2) R = Cl



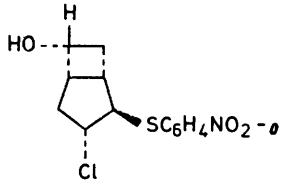
(3) R^1 = H; R^2 = SPh; R^3 = Cl
(4) R^1 = H; R^2 = $SC_6H_4NO_2$-*p*; R^3 = Cl
(5) R^1 = H; R^2 = $SC_6H_4NO_2$-*o*; R^3 = Cl
(6) R^1 = R^3 = Cl; R^2 = SPh
(7) R^1 = R^3 = Cl; R^2 = $SC_6H_4NO_2$-*p*
(8) R^1 = R^3 = Cl; R^2 = $SC_6H_4NO_2$-*o*
(9) R^1 = H; R^2 = $SOC_6H_4NO_2$-*o*; R^3 = Cl
(10) R^1 = H; R^2 = $SO_2C_6H_4NO_2$-*o*; R^3 = Cl
(11) R^1 = R^3 = Cl; R^2 = $SOC_6H_4NO_2$-*o*
(12) R^1 = R^3 = Cl; R^2 = $SO_2C_6H_4NO_2$-*o*



(13) R^1 = R^2 = H
(14) R^1 = NO_2; R^2 = H
(15) R^1 = H; R^2 = NO_2



(16)

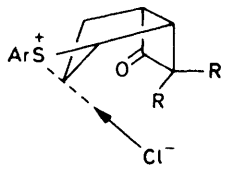


(17)

preferred isomer (20) can be conveniently monitored by the shift of the resonance of the $CHCl_2$ proton [for the ester (18), δ 6.58; for the ester (20), δ 6.10].

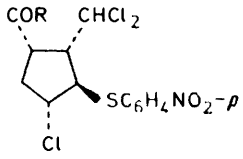
Oxidation ketone of the (5) with an excess of *m*-

chloroperoxybenzoic acid afforded the sulphone lactone (23). When 1—2 equiv. of this oxidising agent was employed, mixtures of compounds were obtained from



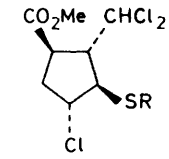
FIGURE

which the lactones (22) and (23), the sulphoxide (9), and the sulphone (10) were obtained. In contrast, *m*-chloroperoxybenzoic acid oxidation of the trichloro-



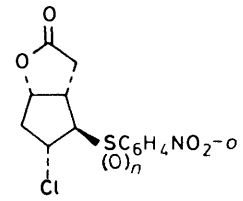
(18) R = OMe

(19) R = N



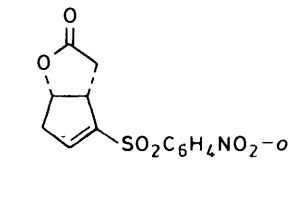
(20) R = $SC_6H_4NO_2$-*o*

(21) R = $SC_6H_4NO_2$-*p*



(22) *n* = 0

(23) *n* = 2



(24)

ketone (8) gave only the sulphoxide (11) and/or the sulphone (12). No lactonic products were obtained.

Finally, reaction of the sulphone (23) with triethylamine led smoothly to the αβ-unsaturated sulphone (24). The stability of the corresponding sulphide (22) under the same reaction conditions indicates that the sulphone moiety is essential for dehydrohalogenation.

EXPERIMENTAL

M.p.s were determined by the capillary tube method. ^{1}H N.m.r. spectra were recorded on a Varian EM-360 or Perkin-Elmer R32 spectrometer in $CDCl_3$ unless otherwise stated. Column chromatography was performed using silica gel M.F.C.; t.l.c. was accomplished using silica gel G (Merck). Anhydrous magnesium sulphate was used as the drying agent for solutions in organic solvents. Petroleum refers to the fraction boiling at 60—80 °C.

Reaction of the Ketones (1) *and* (2) *with the Sulphenyl Chlorides* (13)—(15).—To a solution of the freshly distilled ketone (1) or (2) (0.15 mol) in acetonitrile (50 ml) was added slowly the sulphenyl chloride (13) or (14) in acetonitrile (50 ml). After 2 h at room temperature the solvent was removed *in vacuo* and the solid residue was triturated with petroleum and diethyl ether. Reaction of the ketone (1) or (2) with the sulphenyl chloride (15) was conducted in the same way except that the reaction mixture was refluxed for 1 h. ^{1}H N.m.r. data for these compounds are recorded in Table 1, while other data are in Table 2.

3-endo-7,7-*Trichloro*-2-exo-(2-*nitrophenylsulphinyl*)*bicyclo*[3.2.0]*heptan*-6-*one* (11).—85% *m*-Chloroperoxybenzoic acid (0.006 25 mol, 1.08 g) in chloroform (20 ml) was added to 3,7,7-trichloro-2-(2-nitrophenylthio)bicyclo[3.2.0]-heptan-6-one (8) (0.005 mol, 1.83 g) in chloroform (50 ml) and the mixture was refluxed for 1 h. The resulting solution was stirred with water (50 ml) and sodium hydrogencarbonate (5 g) for 24 h. Chloroform (50 ml) was added and the organic phase was washed twice with water (25 ml). After drying the solvent was removed and the residue was chromatographed over silica (150 g) using dichloromethane as the eluant. The starting material (8) and the sulphone (12) were eluted first followed by the sulphoxide (11) which was recrystallised from carbon tetrachloride–dichloromethane (yield 65%), m.p. 194 °C; δ 8.50—7.70 (4 H, m, C_6H_4), 4.58 (1 H, m, H-2), 4.28—3.96 (2 H, m, H-3 and H-5), 3.70 (1 H, m, H-1), and 2.97—2.13 (2 H, m, H_2-4) (Found:

TABLE 1

^{1}H N.m.r. data for the bicycloheptanones (3)—(8) (multiplicity in parentheses with *J*/Hz)

Compound	Chemical shift δ [multiplicity: observed coupling constants (Hz)]						
	H-1	H-2	H-3	H_2-4	H-5	H_2-7	Aromatic
(3)	3.04 (m)	4.06 (s)	4.42 (m)	2.73—2.55 (m)	3.90 (m)	3.41 (m)	7.46—7.25
(4)	3.10 (m)	4.24 (s)	4.44 (m)	2.75—2.59 (m)	3.88 (m)	4.39 (m)	8.20—7.42
(5)	3.16 (m)	4.20 (s)	4.43 (m)	2.69—2.59 (m)	3.90 (m)	3.52 (m)	8.24—7.26
(6)	3.43 (dd: 8,2)	4.33—4.04 (m)	4.33—4.04 (m)	2.73—2.53 (m)	4.33—4.04 (m)		7.54—7.30
(7)	3.47 (dd: 8,2)	4.43—4.19 (m)	4.43—4.19 (m)	2.82—2.61 (m)	4.42—4.19 (m)		8.24—7.48
(8)	3.57 (dd: 8,2)	4.43—4.19 (m)	4.43—4.19 (m)	2.83—2.64 (m)	4.43—4.19 (m)		8.26—7.25

TABLE 2

Bicyclic ketones (3)—(8) formed from addition of the sulphenyl chlorides (13)—(15) to the unsaturated ketones (1) and (2)

Compound	Recrystallisation solvent	Yield (%)	M.p. (°C)	Analysis (%) Found C	Found H	Found N	Required C	Required H	Required N	Formula
(3)	CH_2Cl_2–petroleum (40—60 °C)	83	71.5—72.5	61.7	5.2		61.8	5.2		$C_{13}H_{13}ClOS$
(4)	$CHCl_3$–CCl_4	82	145.5—146	52.4	4.0	4.8	52.3	4.1	4.7	$C_{13}H_{12}NClO_3S$
(5)	$CHCl_3$–CCl_4	77	120—121	52.1	3.9	4.7	52.3	4.1	4.7	$C_{13}H_{12}NClO_3S$
(6)	CH_2Cl_2–petroleum (40—60 °C)	92	71—71.5	48.5	3.4		48.2	3.5		$C_{13}H_{11}Cl_3OS$
(7)	$CHCl_3$–CCl_4	87	166	42.8	2.7	4.1	42.6	2.8	3.8	$C_{13}H_{10}NCl_3O_3S$
(8)	$CHCl_3$–CCl_4	83	125—125.5	42.8	2.8	4.0	42.6	2.8	2.8	$C_{13}H_{10}NCl_3O_3S$

C, 40.8; H, 2.6; N, 3.7. $C_{13}H_{10}Cl_3NO_4S$ requires C, 40.8; H, 2.7; N, 3.5%).

3-endo-7,7-*Trichloro*-2-exo-(2-*nitrophenylsulphonyl*)*bicyclo*[3.2.0]*heptan*-6-*one* (12).—The same reaction conditions as described above were employed except that 85% *m*-chloroperoxybenzoic acid (0.015 mol, 2.59 g) was used. Recrystallisation from carbon tetrachloride in dichloromethane gave the sulphone (12) (yield 91%), m.p. 187 °C; δ 8.22—7.88 (4 H, m, C_6H_4), 5.06 (1 H, t, *J* 3 Hz, H-2), 4.87 (1 H, m, H-3), 4.49 (1 H, td, *J* 9, 3 Hz, H-5), 4.08 (1 H, m, H-1), and 2.87—2.46 (2 H, m, H_2-4) (Found: C, 39.2; H, 2.5; N, 3.6. $C_{13}H_{10}Cl_3NO_5S$ requires C, 39.2; H, 2.5; N, 3.5%).

3-endo-*Chloro*-2-exo-(2-*nitrophenylsulphinyl*)*bicyclo*[3.2.0]-*heptan*-6-*one* (9) *and* 7-endo-*Chloro*-6-exo-(2-*nitrophenylthio*)-2-*oxabicyclo*[3.3.0]*octan*-3-*one* (22).—3-Chloro-2-(2-nitrophenylthio)bicyclo[3.2.0]heptan-6-one (5) (0.005 mol, 1.49 g) was dissolved in chloroform (20 ml) and 85% *m*-chloroperoxybenzoic acid (0.006 25 mol, 1.08 g) was added. After stirring for 2 h at room temperature the mixture was worked up as above and chromatographed over silica (175 g) with ethyl acetate–petroleum (1 : 3). From the first fractions was obtained a solid which was recrystallised from carbon tetrachloride in chloroform to furnish the *sulphoxide* (9) (yield 43%), m.p. 144 °C; δ 8.48—7.65 (4 H, m, C_6H_4), 4.57 (1 H, m, H-2), 4.05—3.14 (5 H, m, H-1, H-3, H-5, and H_2-7), and 2.68—2.43 (2 H, m, H_2-4) (Found: C, 49.7; H, 3.8; N, 4.5. $C_{13}H_{12}ClNO_4S$ requires C, 49.8; H, 3.9; N, 4.5%). From later fractions was obtained a solid which was recrystallised from carbon tetrachloride in chloroform to give the *lactone* (22) (yield 39%), m.p. 201 °C; δ [$(CD_3)_2SO$] 8.41—7.76 (4 H, m, C_6H_4), 4.80 (1 H, m, H-1), 4.04—3.60 (2 H, m, H-6 and H-7), and 3.13—1.98 (4 H, m, H-4, H-5, and H_2-8) (Found: C, 49.4; H, 3.8; N, 4.4. $C_{13}H_{12}ClNO_4S$ requires C, 49.8; H, 3.9; N, 4.5%).

3-*Chloro*-2-(2-*nitrophenylsulphonyl*)*bicyclo*[3.2.0]*heptan*-6-*one* (10).—The same reaction conditions as above were used except that 85% *m*-chloroperoxybenzoic acid (0.012 mol, 2.1 g) was added over 1.5 h at −10 °C and the reaction mixture was stirred for 1.5 h at this temperature. Work-up as described above gave a residue which was chromatographed over silica (175 g) using ethyl acetate–petroleum (1 : 1). From the first fractions was isolated a solid which was recrystallised from carbon tetrachloride in chloroform to furnish the sulphone (10) (yield 16%), m.p. 158—159 °C; δ 8.23—7.77 (4 H, m, C_6H_4), 4.91—4.69 (2 H, m, H-2 and H-3), 4.00 (1 H, m, H-5), 3.68—3.37 (3 H, m, H-1 and H_2-7), and 2.81—2.57 (2 H, m, H_2-4) (Found: C, 47.2; H, 3.8; N, 4.3. $C_{13}H_{12}ClNO_5S$ requires C, 47.4; H, 3.7; N, 4.3%). From later fractions was isolated the *sulphone* (23) (yield 64%), identical to authentic material (see below).

7-endo-*Chloro*-6-exo-(2-*nitrophenylsulphonyl*)-2-*oxabicyclo*[3.3.0]*octan*-3-*one* (23).—The same reaction conditions as above were used except that 85% *m*-chloroperoxybenzoic acid (0.02 mol, 3.45 g) was added and the reaction mixture was refluxed for 2 h. Work-up in the usual manner gave a solid which was recrystallised from ethyl acetate–petroleum to give the *sulphone* (23) (yield 86%), m.p. 200 °C (decomp.); δ [$(CD_3)_2SO$] 8.33—7.94 (4 H, m, C_6H_4), 5.10 (1 H, m, H-1), 4.86—4.48 (2 H, m, H-6 and H-7), 3.41 (1 H, m, H-5), and 3.12—2.16 (4 H, m, H_2-4 and H_2-8) (Found: C, 44.9; H, 3.5; N, 4.1. $C_{13}H_{12}ClNO_6S$ requires C, 45.2; H, 3.5; N, 4.1%).

3-endo-*Chloro*-2-exo-(2-*nitrophenylthio*)*bicyclo*[3.2.0]-*heptan*-6-endo-*ol* (17).—Bicyclo[3.2.0]hept-2-en-6-*endo*-ol (16) (0.002 mol, 0.22 g) in dry acetonitrile (10 ml) was mixed with 2-nitrobenzenesulphenyl chloride in dry acetonitrile (10 ml) and refluxed for 2 h. After removal of the solvent *in vacuo*, the mixture was chromatographed over silica (50 g) using ethyl acetate–petroleum (1 : 4) to give a solid product which was recrystallised from ethyl acetate–petroleum (yield 83%), m.p. 112—113 °C; δ 8.21—7.22 (4 H, m, C_6H_4), 4.56—4.24 (2 H, m, H-2 and H-3), 3.89 (1 H, m, H-6), 3.32 (1 H, m, H-5), 2.92 (1 H, m, H-1), 2.78—2.33 (4 H, m, H_2-4 and H_2-7), and 2.17 (1 H, s, OH) (Found: C, 51.9; H, 4.6; N, 4.6. $C_{13}H_{14}ClNO_3S$ requires C, 52.1; H, 4.7; N, 4.7%).

Methyl 4-*Chloro*-c-2-(*dichloromethyl*)-t-3-(4-*nitrophenylthio*)*cyclopentane*-r-1-*carboxylate* (18).—3,7,7-Trichloro-2-(4-nitrophenylthio)bicyclo[3.2.0]heptan-6-one (7) (0.0025 mol, 0.92 g) in methanol (90 ml) and water (10 ml) was stirred with iron (0.008 12 mol, 0.45 g) and ammonium chloride (0.0011 mol, 0.06 g) for 12 h at room temperature. The iron was filtered off and washed with methanol (25 ml). The solutions were combined and the solvents evaporated to leave a solid which was recrystallised from carbon tetrachloride methylene chloride to give the ester (18) (73%), m.p. 102.5 °C; δ 8.15—7.25 (4 H, m, C_6H_4), 6.58 (1 H, d, *J* 7 Hz, $CHCl_2$), 4.38—4.01 (2 H, m, H-3 and H-4), 3.75 (3 H, s, OMe), 3.42 (1 H, m, H-1), 3.09 (1 H, m, H-2), and 2.73—2.52 (2 H, m, H_2-5) (Found: C, 42.2; H, 3.6; N, 3.5. $C_{14}H_{14}Cl_3NO_4S$ requires C, 42.2; H, 3.5; N, 3.5%).

c-4-*Chloro*-c-2-(*dichloromethyl*)-r-1-*piperidinocarbonyl*-t-3-(4-*nitrophenylthio*)*cyclopentane* (19).—3,7,7-Trichloro-2-(4-nitrophenylthio)bicyclo[3.2.0]heptan-6-one (7) (0.0025 mol, 0.92 g) in dichloromethane (25 ml) was treated with piperidine (0.025 mol, 2.1 g, 2.5 ml) in dichloromethane (25 ml). After removal of the solvent the residue was purified by chromatography over silica (50 g) using ethyl acetate–petroleum (1 : 1) to give a solid which was recrystallised from ethyl acetate–petroleum to yield the *amide* (19) (yield 78%), m.p. 138—140 °C; δ 8.14—7.21 (4 H, m, C_6H_4), 6.48 (1 H, d, *J* 8 Hz, $CHCl_2$), 4.51—4.17 (2 H, m, H-3 and H-4), 3.72—3.34 (5 H, m, H-1 and 2 × NCH_2), 2.91 (1 H, m, H-2), 2.70—2.46 (2 H, m, H_2-5), and 1.77—1.48 (6 H, m, 3 × CH_2) (Found: C, 47.7; H, 4.7; N, 6.3. $C_{18}H_{21}Cl_3N_2O_3S$ requires C, 47.9; H, 4.7; N, 6.2%).

Methyl t-4-*Chloro*-t-2-(*dichloromethyl*)-c-3-(2-*nitrophenylthio*)*cyclopentane*-r-1-*carboxylate* (20).—3,7,7-Trichloro-2-(2-nitrophenylthio)bicyclo[3.2.0]heptan-6-one (8) (0.0025 mol, 0.92 g) in methanol (20 ml) was added to methanol (30 ml) containing sodium (*ca.* 0.5 g). The volume of the mixture was reduced to *ca.* 10 ml by removal of solvent and water (50 ml) was added. The precipitate was filtered off, washed with water, dried, and recrystallised from dichloromethane–carbon tetrachloride to give the *ester* (20) (88%), m.p. 101—101.5 °C; δ 8.22—7.25 (4 H, m, C_6H_4), 6.10 (1 H, d, *J* 7 Hz, $CHCl_2$), 4.28 (1 H, m, H-4), 4.03 (1 H, m, H-3), 3.77 (3 H, s, OMe), 3.46 (1 H, m, H-1), 3.21 (1 H, m, H-2), and 2.65—2.39 (2 H, m, H_2-5) (Found: C, 42.2; H, 3.6; N, 3.5. $C_{14}H_{14}Cl_3NO_4S$ requires C, 42.2; H, 3.5; N, 3.5%).

Methyl t-4-*Chloro*-t-2-(*dichloromethyl*)-c-3-(4-*nitrophenylthio*)*cyclopentane*-r-1-*carboxylate* (21).—Treatment of the ketone (7) with sodium methoxide in the manner described above gave the ester (21) (84%), m.p. 102.5—103 °C; δ 8.20—7.48 (4 H, m, C_6H_4), 6.08 (1 H, d, *J* 6 Hz, $CHCl_2$), 4.26 (1 H, m, H-4), 3.95 (1 H, m, H-3), 3.77 (3 H, s, OMe), 3.41 (1 H, m, H-1), 3.17 (1 H, m, H-2), and 2.64—2.37 (2 H, m, H_2-4) (Found: C, 42.0; H, 3.6; N, 3.5. $C_{14}H_{14}Cl_3NO_4S$ requires C, 42.2; H, 3.5; N, 3.5%).

6-(2-*Nitrophenylsulphonyl*)-2-*oxabicyclo*[3.3.0]*oct*-6-*en*-3-

one (24).—The sulphone (23) (0.001 mol, 0.345 g) was dissolved in dichloromethane (10 ml) and triethylamine (0.002 mol, 0.3 ml) and stirred for 3 h at room temperature. The solvents were evaporated and the residue was chromatographed over silica (50 g) using ethyl acetate–petroleum (1 : 1) and the solid obtained was recrystallised from ethyl acetate–petroleum to give the sulphone (24) (yield 82%), m.p. 155 °C; δ [$(CD_3)_2SO$] 8.27—7.87 (4 H, m, C_6H_4), 6.95 (1 H, m, H-7), 4.55—4.44 (2 H, m, H-1 and H-5), and 4.02—2.79 (4H, H_2-4 and H_2-8) (Found: C, 50.4; H, 3.8; N, 4.5. $C_{13}H_{11}NO_6S$ requires C, 50.5; H, 3.6; N, 4.5%).

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