Unusual Regio- and Stereo-chemistry in the Reaction of Methyl (*E*)- and (*Z*)-β-Styryl Sulphone with Pyrrolidin-1-yl-4-t-butylcyclohexene

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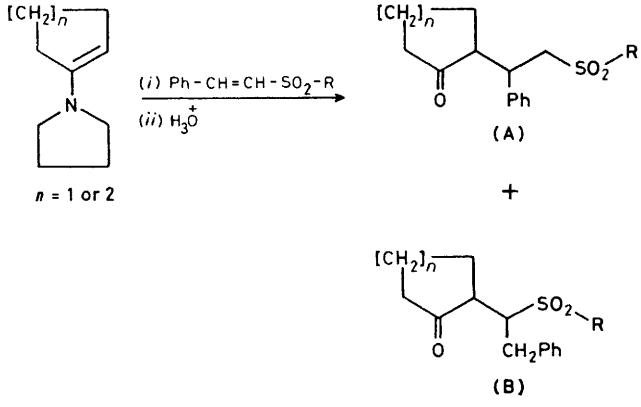
Pyrrolidin-1-yl-4-t-butylcyclohexene undergoes both antiparallel and parallel attack in the reaction with methyl (*E*)- and (*Z*)-β-styryl sulphone. Moreover, the addition is regiospecific with respect to each starting sulphone: in fact the *Z*-isomer reacts almost exclusively at the carbon atom α to SO_2, whilst the *E*-isomer reacts, although in poor yield, only at the β-carbon. The structures of the 2-substituted-4-t-butylcyclohexanones, obtained by hydrolysis of the reaction mixtures, have been established by n.m.r. analysis and by the results of equilibration reactions in acidic and/or basic media.

It is known that the enamines of cycloalkanones react with electrophilic olefins [1] by a stereospecific antiparallel attack.[2] Parallel attacks of these olefins to enaminic systems have been noticed only when steric hindrance inhibits the antiparallel approach.[3] It is noteworthy that, when the electrophilic carbon atom of the olefin bears a hindering group, either antiparallel or parallel attack occurs in such a stereospecific way as to determine a definite configuration of this carbon atom in the reaction products, *i.e.* trisubstituted enamines.[2-4,†]

Nevertheless, we have noticed two unusual results during recent research work in our laboratories. In the first, 1-morpholino-4-t-butylcyclohexene undergoes both antiparallel and parallel attack with 1-nitropropene, in spite of the lack of any steric hindrance for antiparallel attack.[4] Second, alkyl and aryl β-styryl sulphones react with pyrrolidin-1-yl-cycloalkenes in a non-regiospecific way to give, after hydrolysis, ketones (A) and (B) (Scheme 1).[5]



SCHEME 1

In order to obtain further information about this unexpected behaviour, we have investigated the reactions of pyrrolidin-1-yl-4-t-butylcyclohexene with methyl (*E*)- and (*Z*)-β-styryl sulphone.

† For the meaning of parallel and antiparallel attack see: E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison, 'Conformational Analysis,' J. Wiley & Sons, Inc., London, 1965, p. 309; J. Valls and E. Toromanoff, *Bull. Soc. chim. France*, 1961, 758.

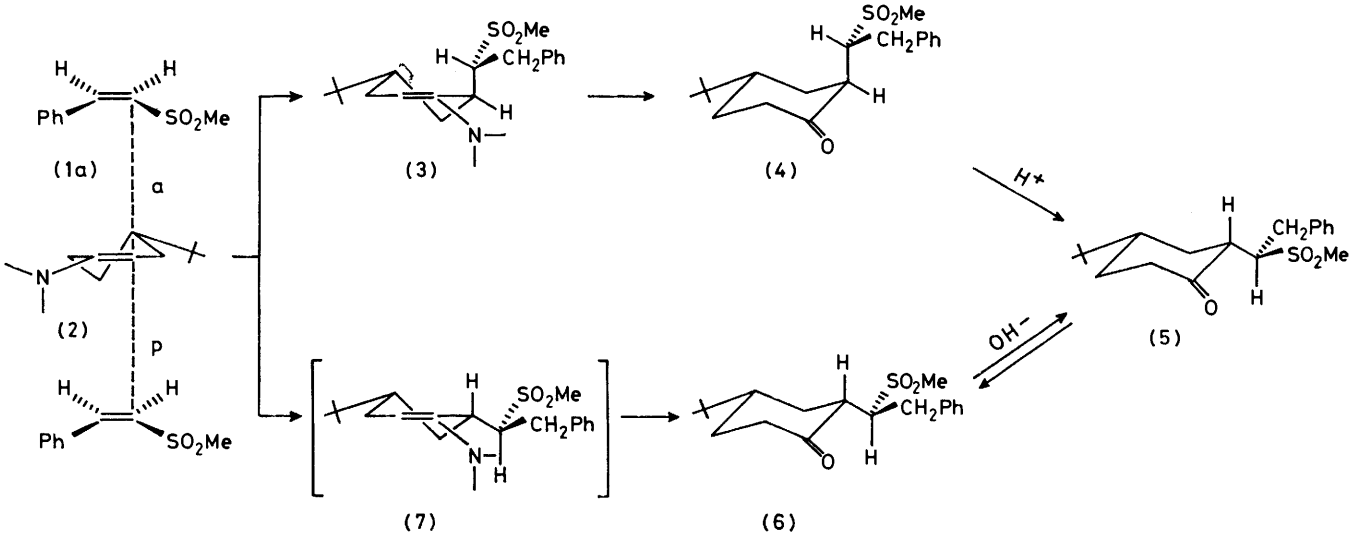
RESULTS AND DISCUSSION

The reactions were performed in refluxing acetonitrile and the results were very different from those previously reported as regards the regiospecificity.[5] In fact, the *Z*-sulphone (1a) reacted in 50% yield to furnish, after hydrolysis, almost exclusively an isomeric mixture of type (B) ketones. On the other hand, the *E*-sulphone (1b) reacted only in 20% yield to give isomeric ketones of type (A); the remaining 80% was recovered unchanged. This regiospecificity relating to the *E*- or *Z*-configuration of the reagent has not previously been noticed, and at present the reasons for such a relation are rather obscure. Compounds of type (A) and (B) are easily distinguished from their ^1H n.m.r. spectra, which clearly show the signals of the CH_2SO_2 [type (A)] or $CHSO_2$ [type (B)] groups.[5] The structures of each diastereoisomeric ketone were established by acidic and/or basic equilibration, as reported below. The reaction mixture obtained from the *Z*-sulphone (1a) furnished, after cooling, an adduct with m.p. 142 °C (27% yield) assigned as a trisubstituted enamine. Thus the i.r. spectrum shows at 1 650 cm^{-1} a sharp band due to an enamine double bond, and the ^1H n.m.r. spectrum shows at δ 5.10—4.60 the absorption of the vinyl proton. This enamine gave, by hydrolysis under non-equilibrating conditions, a ketone of the type (B), m.p. 111 °C, which was completely converted by 10% hydrochloric acid into a more stable ketone with m.p. 121 °C. These results allow us to assign the structure of (2*R**,α*R**)-*trans*-pyrrolidin-1-yl-2-[α-(methylsulphonyl)-β-phenylethyl]-4-t-butylcyclohex-6-ene (3) to the isolated enamine and the structures of (2*R**,α*R**)-*trans*- (4) and (2*S**,α*R**)-*cis*-2-[α-(methylsulphonyl)-β-phenylethyl]-4-t-butylcyclohexanone (5) to the ketones with m.p. 111 and 121 °C, respectively. The stereochemistry at C-α is assigned on the basis of the direction of attack of the electrophilic olefin, so that the largest substituent SO_2Me points out of the ring. Obviously the configuration at C-α in ketones (4) and (5) is the same as in the parent enamine (Scheme 2).

When the hydrolysis was performed, under equilibrating conditions, directly on the reaction mixture of (1a) with (2), a new isomeric ketone, m.p. 129—130 °C, having a type (B) structure, was isolated as well as (5).

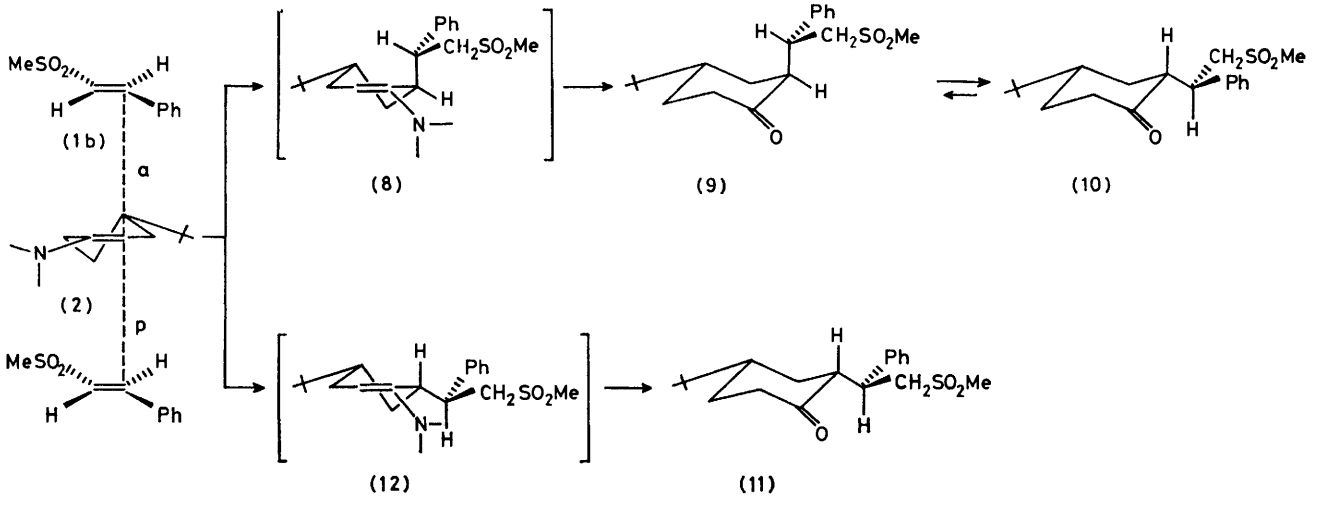
This product is a *cis*-compound since it is stable in acidic media; moreover, in basic media it was partially converted into (5). These results indicate that the ketone with m.p. 129—130 °C and (5) differ only in the configuration at C-α, and therefore the former has structure (6). Such a ketone clearly must originate from the enamine (7), which can be formed only from parallel attack.

The ketone with m.p. 160 °C is stable in acidic and basic media. The other two isomers under the same conditions are both converted into an equilibrium mixture containing 65% of the product with m.p. 176 °C, and 35% of the compound with m.p. 140 °C. Since the benzylic hydrogen atom is not acidic enough to allow epimerization at C-α in basic media, the above interconversion concerns only the configuration at C-2; therefore the products under question must be *cis* (65%) and *trans* (35%) isomers.*



a: antiparallel attack; p: parallel attack

SCHEME 2



a: antiparallel attack; p: parallel attack

SCHEME 3

No enaminic adducts were isolated in the reaction between the *E*-sulphone (1b) and the enamine (2). Therefore the reaction mixture was directly hydrolysed under equilibrating conditions. Three isomeric type (A) ketones with m.p. 140, 176 and 160, °C were isolated in a ratio of 3 : 2 : 1, respectively.

Since the *trans*-ketone with m.p. 140 C° was also isolated from the kinetically controlled hydrolysis of the

* Such a partial *trans–cis* conversion appears unusual; nevertheless another similar case has been reported.[6]

reaction mixture, it must be the (2*S**,α*R**)-isomer (9) deriving from the enamine (8), and the *cis*-compound with m.p. 176 °C must have the (2*R**,α*R**)-configuration (10).

Thus the product with m.p. 160 °C, can only be the (2*R**,α*S**)-*cis*-isomer (11), deriving from an enemine (12) produced by parallel attack. In this case the configuration at C-α of the enamine intermediates (8) and (12), and consequently that of the corresponding ketones, is assigned on the basis of the direction of attack of the olefin leading to adducts in which the phenyl group is *exo* to the carbocyclic ring (Scheme 3).

The ketones of type (A) [(9)—(11)] were also obtained in small amount (3%) in the reaction of the *Z*-sulphone (1a) with (2). In this case their formation could be ascribed to the partial *Z*→*E* isomerization of the starting sulphone in the first reversible step of the reaction, as we have ascertained previously.[5]

EXPERIMENTAL

^{1}H N.m.r. spectra were recorded with a Perkin-Elmer R 12B spectrometer ($SiMe_4$ as internal standard; solutions in $CDCl_3$) and i.r. spectra (Nujol mulls) with a Perkin-Elmer 257 spectrophotometer. For analytical t.l.c., plates were coated with silica gel G (Merck) and developed with benzene–acetone (90 : 10). For chromatographic columns extra-pure silica (Merck; 70—230 mesh ASTM) was used as the stationary phase and benzene–acetone (90 : 10) as eluant.

Reaction of Pyrrolidin-1-yl-4-t-butylcyclohexene (2) *with Methyl* (Z)-β-*Styryl Sulphone* (1a).—The enamine (2) (5 g, 24.1 mmol) and the sulphone (1a) [7] (4.39 g, 24.1 mmol) in dry acetonitrile (25 ml) were refluxed for 24 h. The solution was concentrated *in vacuo* and then diluted with dry diethyl ether. After standing in the freezer for several hours, (2R*,αR*)-trans-*pyrrolidin-1-yl-2-*[α-(*methylsulphonyl*)-β-*phenylethyl*]-4-*t-butylcyclohex-6-ene* (3) was collected and washed with dry diethyl ether (2.5 g, 27%), m.p. 142 °C (Found: C, 70.6; H, 9.2; N, 3.5. $C_{23}H_{35}NO_2S$ requires C, 70.9; H, 9.1; N, 3.6%); $\nu_{max.}$ 1 650 (C=C), and 1 305, 1 290, 1 130, and 1 125 cm^{-1} (SO_2); δ 5.10—4.60 (1 H, m, vinyl-H) and 4.40—3.90 (1 H, m, C*H*SO_2Me). In another run the solution obtained after heating for 24 h was hydrolysed (12 h) at room temperature with 10% hydrochloric acid (15 ml). After dilution with water and extraction with chloroform, the oily residue (8 g) was chromatographed on silica. First fractions gave 4-*t-butylcyclohexanone* (1.80 g) and *methyl* (E)-β-*styryl sulphone* (1) (2 g). Further elutions furnished a small amount (0.24 g, 3% yield) of the isomeric type (A) *ketones* (9)—(11) and finally a mixture of the isomeric cis-2-[α-(*methylsulphonyl*)-β-*phenylethyl*]-4-*t-butylcyclohexanones* (5) and (6) (3.81 g, 47%), m.p. 90—100 °C (Found: C, 67.9; H, 8.3. $C_{19}H_{28}O_3S$ requires C, 67.8; H, 8.4%). This mixture, which showed one spot on t.l.c., furnished after repeated recrystallization from ethanol (2S*, α*R**)-cis-2-[α-(*methylsulphonyl*)-β-*phenylethyl*]-4-*t-butylcyclohexanone* (5) m.p. 121—122 °C (Found: C, 67.8; H, 8.4); $\nu_{max.}$ 1 720 (CO), and 1 300, 1 290, and 1 138 cm^{-1} (SO_2); δ 7.30 (5 H, m, Ar-H), 4.65—4.30 (1 H, dd, C*H*SO_2Me), 2.80—1.30 (10 H, CH_2Ph and aliphatic ring-H), 2.70 (3 H, s, SO_2Me), and 0.85 (9 H, s, CMe_3). From the ethanolic mother-liquor the isomer (2S*, αS*)-cis-2-(α-*methylsulphonyl*-β-*phenylethyl*)-4-t-*butylcyclohexanone* (6) was isolated, m.p. 129—130 °C (Found: C, (67.9; H, 8.4; $\nu_{max.}$ 1 704 (CO), and 1290 and 1 128 cm^{-1} (SO_2); δ 7.4 (5 H, m, Ar-H), 4.45—4 (1 H, m, C*H*SO_2Me), 2.75—1.20 (10 H, CH_2Ph and aliphatic ring-H), 2.60 (3 H, s, SO_2Me), and 0.90 (9 H, s, CMe_3). The ketones (5) and (6) were present in the original mixture with m.p. 90—100 °C in the ratio 6 : 5, as ascertained by integration of the ^{1}H n.m.r. signals of the SO_2Me groups.

Kinetically Controlled Hydrolysis of the Enamine (3).—A solution of the enamine (3) (1.95 g, 5 mmol) in acetonitrile (200 ml) was treated with 30% acetic acid (1 ml, 5 mmol). After 3 h at room temperature the solution was concentrated under reduced pressure without heating, diluted with water, and extracted with chloroform. Removal of the solvent furnished (2R*, αR*)-trans-2-[α-(*methylsulphonyl*)-β-*phenylethyl*]-4-*t-butylcyclohexanone* (4) (1.60 g, 96%), m.p. 111 °C (from benzene–light petroleum) (Found: C, 67.8; H, 8.5. $C_{19}H_{28}O_3S$ requires C, 67.8; H, 8.4%); $\nu_{max.}$ 1 710 (CO), and 1 310, 1 298, and 1 135 cm^{-1} (SO_2); δ 7.40 (5 H, m, Ar-H), 4.38—3.92 (1 H, m, C*H*SO_2Me), 2.80—1.30 (10 H, CH_2Ph and aliphatic ring-H), 2.60 (3 H, s, SO_2Me), and 0.9 (9 H, s, CMe_3).

Acidic Equilibration of the Ketone (4).—An ethanolic solution of (4) (0.500 g in 20 ml) was treated at room temperature with 10% hydrochloric acid (2.0 ml). After 12 h the solution was concentrated *in vacuo*, diluted with water, and extracted with chloroform. The solid residue (0.500 g; m.p. 121 °C) was found to be identical with the ketone (5), obtained by acidic hydrolysis of the reaction mixture of (2) with (1a).

Attempted Acidic Equilibration of the Ketone (6).—The ketone (6) was recovered unchanged when treated for 12 h in ethanol with 10% hydrochloric acid.

Basic Equilibration of the Ketones (5) *and* (6).—An ethanolic solution of (5) or (6) (0.500 g in 20 ml) was treated at room temperature with 10% ethanolic potassium hydroxide (10 ml). After 1 h the solution was acidified with 10% hydrochloric acid, diluted with water, and extracted with chloroform. Removal of the solvent furnished an oily residue: $\nu_{max.}$ 1 720 and 1 704 cm^{-1} (CO); δ 2.70 and 2.60 (SO_2Me) corresponding to (5) and (6) in a ratio of 3 : 2, respectively.

Reaction of Pyrrolidin-1-yl-4-t-butylcyclohexene (2) *with Methyl* (E)-β-*Styryl Sulphone* (1b).—The enamine (2) (3.80 g, 18.3 mmol) and the sulphone (1b) [8] (3.33 g, 18.3 mmol) in dry acetonitrile (20 ml) were refluxed for 24 h. After cooling, the solution was hydrolysed (12 h) at room temperature with 10% hydrochloric acid (10 ml), diluted with water and extracted with chloroform. The residue (6 g) was chromatographed on silica. First fractions gave 4-*t-butylcyclohexanone* (2.20 g) and *methyl* (E)-β-*styryl sulphone* (1b) (2.60 g); further elution furnished (2R*, αR*)-cis-2-[α-*phenyl*-β-(*methylsulphonyl*)*ethyl*]-4-*t-butylcyclohexanone* (10) (0.61 g, 10%), m.p. 176 °C (from ethanol) (Found: C, 67.9; H, 8.6. $C_{19}H_{28}O_3S$ requires C, 67.8; H, 8.4%); $\nu_{max.}$ 1 705 (CO), and 1 300, 1 270, and 1 120 cm^{-1} (SO_2); δ 7.3 (5 H, m, Ar-H), 3.95—3.35 (3 H, m, C*H*Ph and C$H_2$$SO_2$Me), 3.10—1.10 (8 H, aliphatic ring-H), 2.58 (3 H, s, SO_2Me), and 0.9 (9 H, s, CMe_3). Subsequent fraction provided the (2S*,αR*)-trans-*isomer* (9) (0.40 g, 6.5%), m.p. 140 °C (from ethanol) (Found: C, 67.8; H, 8.5); $\nu_{max.}$ 1 705 (CO) and 1 290, 1 275, and 1 130 cm^{-1} (SO_2); δ 7.3 (5 H, m, Ar-H), 3.9—3.0 (3 H, complex, C*H*Ph and C$H_2$$SO_2$Me), 2.80—1.10 (8 H, aliphatic ring-H), 2.30 (3 H, s, SO_2Me), and 0.75 (9 H, s, CMe_3). The last fraction afforded the (2R*,αS*)-cis-*isomer* (11) (0.20 g, 3.3%), m.p. 160 °C (from ethanol)

(Found: C, 67.8; H, 8.3); $\nu_{max.}$ 1 700 (CO), and 1 290, 1 278, and 1 128 cm^{-1} (SO_2); δ 7.3 (5 H, m, Ar-H), 3.7—3.4 (3 H, m, C*H*Ph and CH_2SO_2Me), 2.70—1.0 (8 H, aliphatic ring-H), 2.5 (3 H, s, SO_2Me), and 0.80 (9 H, s, CMe_3).

Acidic Equilibration of Ketones (9) *and* (10).—The ethanolic solution of the ketone (9) or (10) (0.50 g in 40 ml) was treated with 10% hydrochloric acid (2.0 ml). After 12 h at room temperature, the solution was concentrated *in vacuo*, diluted with water, and extracted with chloroform. The solid residue gave the following n.m.r. analysis: δ 2.58 and 2.30 (SO_2Me), corresponding to (10) and (9) in a ratio of 3 : 2.

Under the same conditions the ketone (11) was recovered unchanged.

Basic Equilibration of Ketones (9) *and* (10).—The ketone (9) or (10) (1 g) in ethanol (100 ml) was treated with 10% ethanolic potassium hydroxide (20 ml) and kept for 12 h at room temperature. The solution was acidified, concentrated *in vacuo*, diluted with water, and extracted with chloroform. The residue (0.95 g) was chromatographed on silica to furnish the pure ketones (10) (0.56 g) and (9) (0.39 g).

Under the same conditions the ketone (11) was recovered unchanged.

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