Stereoselective Olefin Formation from the Dehydration of 1-(*p*-Alkoxyphenyl)-1,2-diphenylbutan-1-ols: Application to the Synthesis of Tamoxifen

Raymond McCague
Drug Development Section, Cancer Research Campaign Laboratory, Institute of Cancer Research, Clifton Avenue, Sutton, Surrey SM2 5PX

Acid-catalysed dehydration of either diastereoisomer of a 1-(*p*-alkoxyphenyl)-1,2-diphenylbutan-1-ol gives mainly the *Z* isomer of the but-1-ene *via* a common carbenium ion intermediate that can be regenerated by protonation of the (*Z*)- or (*E*)-butene with fluorosulphonic acid. Highly stereoselective *syn* eliminations were achieved by treatment of the butan-1-ols with base and carbon disulphide but dehydrations using *N,N,N*-triethylammonio-*N'*-methoxycarbonylsulphamidate proceeded mainly *via* a carbenium ion. Aspects of the stereoselectivity of the reactions are discussed. The methods can be applied to give simple stereoselective syntheses of the anti-cancer drug tamoxifen.

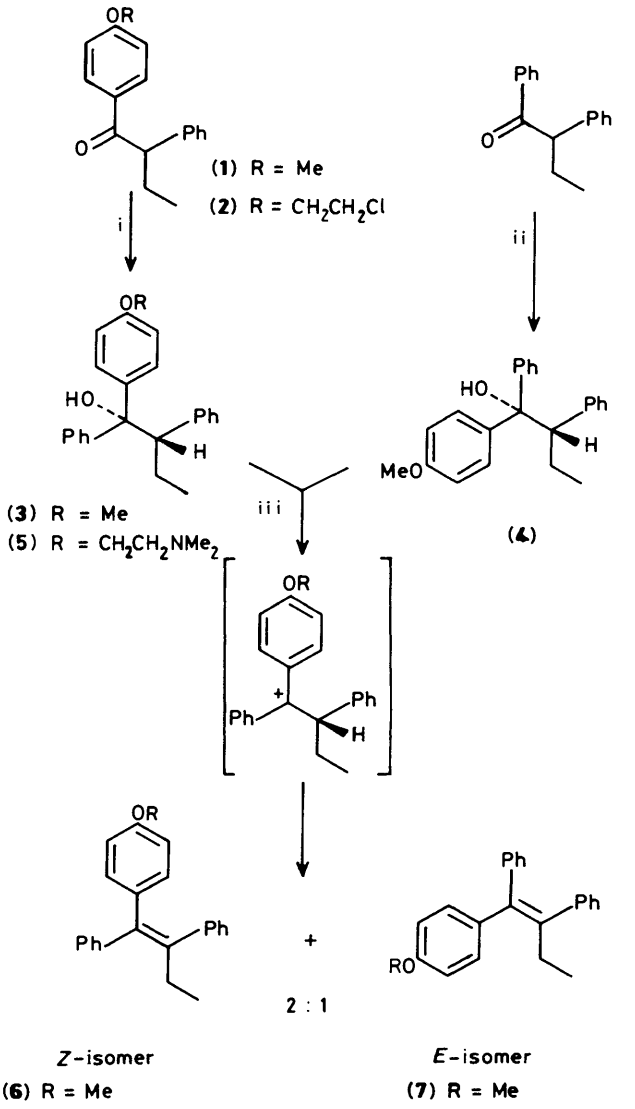
The dehydration of an easily synthesized 1,1,2-triarylbutan-1-ol is a key step in an important synthesis [1] of tamoxifen {*Z*-1-[*p*-(2-dimethylaminoethoxy)phenyl]-1,2-diphenylbut-1-ene} (**8**), a drug developed by I.C.I. and currently in clinical use for the treatment of hormone-dependent breast cancer.[2] However, this synthesis gives a mixture of *Z* and *E* isomers which are difficult to separate and of which only the *Z* isomer has the antioestrogenic activity required for pharmaceutical use. Moreover, the *E* isomer has oestrogenic properties which would oppose the action of tamoxifen.[3,4] A stereospecific synthesis of tamoxifen involving carbometallation of a substituted alkyne has been reported [5] but the procedure is somewhat lengthy and therefore simpler stereoselective approaches are preferable. Very recently, it has been reported that precursors of tamoxifen can be prepared with good stereoselectivity (up to 9:1 *Z*:*E*) by a low-valent titanium mediated coupling of substituted benzophenones with propiophenone,[6] but the applicability of this route to the synthesis of variously substituted analogues is yet to be established. On the other hand, dehydration of 1,1,2-triarylbutan-1-ols is a route that has proven applicability to the synthesis of a considerable variety of tamoxifen analogues.[7] Although the preparation of tamoxifen by this method has been reported to yield a 1:1 mixture of *Z* and *E* isomers [8] an analogous preparation of 1-(*p*-methoxyphenyl)-1,2-diphenylbut-1-ene gave a 2:1 mixture of the *Z*(**6**) and *E*(**7**) isomers.[9] It is this unexpected and puzzling stereoselectivity that prompted this investigation.

This paper reports methods for the stereoselective dehydration of 1-(*p*-alkoxyphenyl)-1,2-diphenylbutan-1-ols to derivatives of tamoxifen.

Results and Discussion

The tertiary alcohol (**3**) was easily prepared by reaction of 1-(*p*-methoxy)-2-phenylbutan-1-one (**1**) with phenylmagnesium bromide, and its diastereoisomer (**4**) from 1,2-diphenylbutan-1-one and (*p*-methoxyphenyl)magnesium bromide (Scheme 1). These addition reactions proceeded in accordance with Cram's rule,[10] as reported for corresponding preparations of the dimethylaminoethoxy derivatives [e.g. (**5**)].[11]

Acid-catalysed Dehydration of the Tertiary Alcohols.—Unexpectedly, dehydration of either tertiary alcohol (**3**) or (**4**) by hydrochloric acid in ethanol gave the same 2:1 ratio of olefinic products (**6**) and (**7**) presumably as a result of the dehydration having proceeded by an *E*1 mechanism with a common carbenium ion intermediate.



Scheme 1. *Reagents*: i, PhMgBr, ether; ii, *p*-$MeOC_6H_4MgBr$, ether; iii, HCl (aq), EtOH, 80 °C.

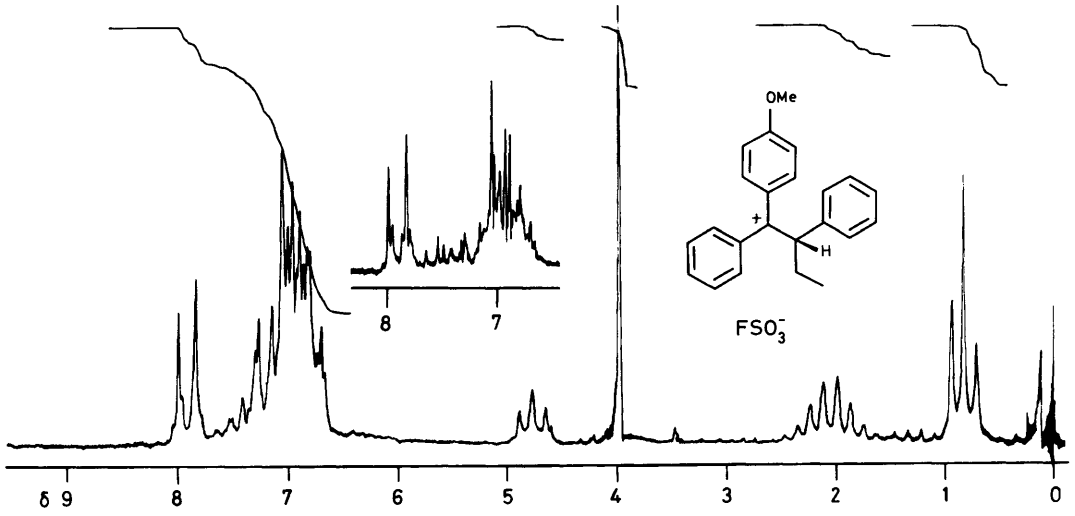


Figure. 60 MHz ^{1}H N.m.r. spectrum of the carbenium ion derived from (*E*/*Z*)-1,2-diphenyl-1-(*p*-methoxyphenyl)but-1-ene (**6**) and (**7**) in $CDCl_3$–FSO_3H (4:1). The inset shows the region of the aromatic protons of the carbenium ion derived from (*E*/*Z*)-1-([$^2H_5$]phenyl)-1-(*p*-methoxyphenyl)-2-phenylbut-1-ene.

On the basis of these observations, it would have been expected that the synthesis of tamoxifen (**8**) by dehydration of the tertiary alcohol (**5**) would have proceeded similarly. However, tamoxifen isomerised in the strongly acidic reaction conditions into an equilibrium 1:1 *Z*/*E* mixture. The methoxy compounds (**6**) and (**7**) did not isomerise under these conditions, probably since the poorly soluble olefinic products precipitated from the reaction mixture as they were formed. On the other hand, the salt formed by protonation of the basic side chain of tamoxifen was very soluble in the polar reaction medium. Nevertheless, using only a brief treatment with a hydrochloric acid solution more dilute than that used to prepare (**6**) and (**7**), tamoxifen (**8**) could be prepared as a 2.1:1 mixture of *Z* and *E* isomers from the tertiary alcohol (**5**).

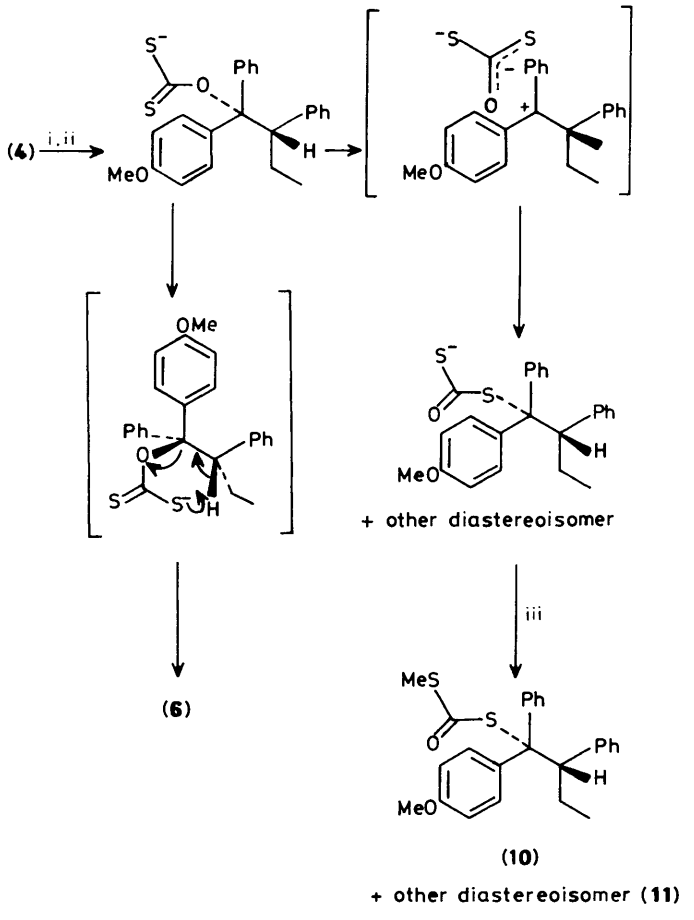
The carbenium ion intermediate could be regenerated from the (*Z*)-or (*E*)-alkenes by their protonation. Thus, treatment of a *Z*/*E* mixture of the methoxy compounds (**6**) and (**7**) with fluorosulphonic acid in chloroform at 0 °C gave a deep orange solution of the carbenium ion. Complete formation of the ion was evident from the ^{1}H n.m.r. spectrum (Figure) in which the proton introduced at C-2 gives a characteristic triplet at δ 4.8. The doublet at δ 7.9 seen also in the spectrum of the carbenium ion of the 1-[$^2H_5$]phenyl analogue is assigned as the signal for the protons *meta* to the methoxy group and its downfield chemical shift is evidence that the oxygen bearing ring provides the principal stabilisation of the ion. Quenching of the solution of the ion with water returned the starting olefin as a 1.5:1 mixture of *Z* and *E* isomers. Similarly, treatment of either *Z* or *E* tamoxifen with fluorosulphonic acid and then quenching with water gave a 1.4:1 *Z*/*E* mixture. Less selectivity was achieved in quenching of the carbenium ion than in the dehydration possibly because of differing solvation of the ions. Nevertheless this process could be useful for converting unwanted *E* isomer into *Z* isomer in analogues where the isomers are separable.

An explanation of the stereoselectivity in the deprotonation is that the stabilisation of the carbenium ion by the oxygen bearing ring is assisted by a weak bonding interaction with the adjacent 2-phenyl ring only in the conformation leading to a product of *Z* stereochemistry. In tamoxifen, the phenyl rings adopt a conformation out of the plane of the double bond[12] such that some overlap of the π-systems of adjacent rings could be expected. It is also interesting to speculate that a similar factor could play a role in governing the stereoselectivity of the low-valent titanium-mediated coupling route[6] although in this case free radical rather than carbenium ion intermediates are most probably involved.

In order to use the stereoselective acid-catalysed dehydration approach for the synthesis of pure (*Z*)-tamoxifen, the preferred route was *via* the chloroethoxy derivative (**9**). Thus, reaction of the ketone (**2**), which is readily prepared in high yield by the Friedel-Crafts acylation of (2-chloroethoxy)benzene with 2-phenylbutanoic acid,[13] with phenylmagnesium bromide gave, after dehydration of the resulting tertiary alcohol, a 2:1 mixture of the (*Z*)-butene (**9**) and its *E* isomer. Although it had been difficult to isolate consistently the *Z* isomer from an equimolar isomer mixture,[9] isolation of pure *Z* isomer from this enriched sample presented no problem in accordance with reported observations.[6] Substitution of the chlorine by dimethylamine is known to give pure (*Z*)-tamoxifen.[9]

Dehydration of the Tertiary Alcohols (**3**) *and* (**4**) *using Base and Carbon Disulphide.*—Since the tertiary alcohols (**3**) and (**4**) could be prepared stereospecifically, then a simple stereospecific synthesis of tamoxifen analogues could be devised if the dehydration could be made to proceed in a stereospecific *syn* manner. It was thought that attempts to achieve this aim would be hampered by a competing *E*1 elimination when the hydroxy group is modified into a better leaving group. Nevertheless, attempts were made to prepare methyl dithiocarbonate *O*-esters (xanthate esters) for use in a Chugaev elimination and hence the tertiary alcohols (**3**) and (**4**) were treated with base, carbon disulphide, and iodomethane. Some elimination took place directly and the olefins were formed (40% yield) in a stereoselective manner. Compound (**3**) gave mainly *E* olefin (4:1, *E*:*Z*) and compound (**4**) gave mainly *Z* olefin (9:1, *Z*:*E*). In addition to olefins, both (**3**) and (**4**) gave a mixture (40% yield) of two further products, formed in a different ratio from (**3**) or (**4**), which gave very similar n.m.r. spectra indicating that they were diastereoisomers. In the case of the product derived from the tertiary alcohol (**4**), the major diastereoisomer could be isolated pure. Comparison of its i.r. spectrum with that of compound (**4**) showed that the product was not a dithiocarbonate *O*-ester but an isomeric dithiocarbonate *S*-ester, most probably (**10**). Thus, there were new absorptions at 1 648 (C=O) and 866 cm^{-1} (C–S). In comparison, *S*-allyl *S*-methyl dithiocarbonate absorbs at 1 658 and 873 cm^{-1} whereas *O*-allyl *S*-methyl dithiocarbonate gives characteristic absorptions for the dithiocarbonate function at 1 217 and 1 060 cm^{-1}.[14]

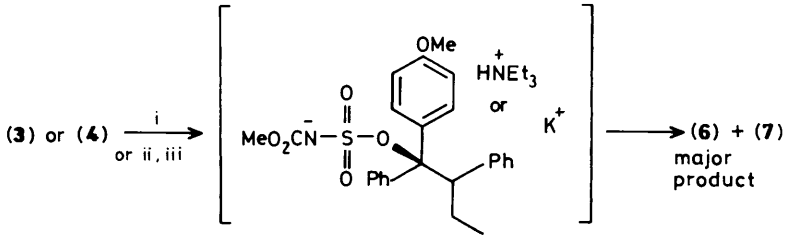
It was found subsequently that the dehydration could be carried out simply by treatment of the tertiary alcohol with base and carbon disulphide. Diastereoisomer (**3**) gave predominantly (*E*)-olefin with high stereoselectivity (12:1, *E*:*Z*) and (**4**) gave the (*Z*)-olefin (21:1, *Z*:*E*). The mechanism of the elimination shown in Scheme 2 in the case of compound (**4**) is most likely to involve cleavage of the dithiocarbonate anion in a cyclic transition state (E_i mechanism). Rearrangement of methyl dithiocarbonate *O*-esters, for example that of cholest-4-en-3β-ol to give dithiocarbonate *S*-esters[15] has been reported, but since omission of methyl iodide and use of a longer reaction time did not significantly increase the yield of olefin (**3**) or (**4**), rearrangement must have taken place at the anion stage and competed with the desired elimination. This rearrangement would most probably involve cleavage of the weak benzylic C–O bond and then recombination to form a C–S bond (Scheme 2). Since the alcohols (**3**) and (**4**) give different ratios of diastereoisomeric dithiocarbonate *S*-esters, rearrangement is probably largely confined to a solvent cage so that there is some retention of configuration. Loss of the benzylic hydrogen atom from the intermediate, instead of recombination, could account for the small amount of *anti*-elimination observed. The alcohol (**4**) did not undergo any isomerisation or elimination in the presence of potassium hydride alone. Thermolysis of the dithiocarbonate *S*-ester (**10**) in xylene at reflux ($t_{\frac{1}{2}}$ *ca.* 5 min) gave a 2:1 mixture of *Z* and *E* isomers of the olefin indicating that its decomposition was by an *E*1 elimination mechanism. The pure (*Z*)-olefin did not isomerise under these conditions.

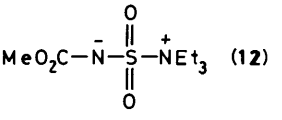


Scheme 2. *Reagents*: i, KH or NaH + imidazole, THF; ii, CS_2; iii, MeI.

It has been reported that dehydration of tertiary alcohols such as 1-methylcyclohexan-1-ol *via* treatment of the potassium salt with carbon disulphide required pyrolysis of the dithiocarbonate *O*-ester salt at 200—250 °C.[16] The exceptionally facile cleavage of the xanthate salt derived from (**3**) or (**4**) is a consequence of stabilisation of the transition state of the elimination by the three aryl substituents. It is unfortunate that at best only a moderate yield (up to 47%) of the olefin was formed. Attempts to improve the yield of olefin by substitution of carbon disulphide by phenyl isocyanate or phenyl isothiocyanate were not successful. Nevertheless, the method could be useful in the synthesis of tamoxifen analogues where difficulty in the separation of isomers of the final product is anticipated. For compound (**6**) at least, the pure isomer was obtained with ease by recrystallisation of the product. Its conversion into (*Z*)-tamoxifen without isomerisation has been reported.[5]

Dehydration of the Tertiary Alcohols (**3**) *and* (**4**) *using* N,N,N-*Triethylammonio*-N′-*methoxycarbonylsulphamidate* (**12**).—Dehydration of *threo*- and *erythro*-[α-$^2H_1$]-1,2-diphenylethanol by the sulphamidate salt (**12**) has been shown to proceed by *syn*-elimination,[17] presumably by a mechanism analogous to the Chugaev elimination of dithiocarbonate *O*-esters. In contrast, dehydration of either the tertiary alcohol (**3**) or (**4**) by this reagent gave a 2.8:1 mixture of the olefins (**6**) and (**7**) consistent with an *E*1 elimination mechanism although, interestingly, the stereoselectivity was slightly better than in acid-catalysed dehydration. It was considered that the initially formed anion (**13**) (Scheme 3) might be protonated by its triethylammonium counter cation and thereby favour cleavage to give a carbenium ion. Preformation of the alkoxides from the





Scheme 3. *Reagents*: i, (**12**), C_6H_6, 50 °C; ii, KH, THF, 22 °C; iii, (**12**), THF, 22 °C.

alcohols (**3**) or (**4**) with potassium hydride circumvented this possible mechanism and also enabled dehydration to be accomplished at room temperature instead of at 50 °C. Under these conditions the alcohols (**3**) and (**4**) gave respectively a 1.6:1 and 3.0:1 mixture of the (*Z*)- and (*E*)-olefins (**6**) and (**7**) indicating that the eliminations still proceeded predominantly by an *E*1 mechanism but that there was some degree of *syn*-elimination.

The course of the dehydration of the triarylbutanols differs from that of 1,2-diphenylethanol since the extra aryl substituent in the former greatly favours formation of a carbenium ion. *trans*-Eliminations from certain steroidal alcohols, presumably *via* carbenium ion intermediates have already been demonstrated.[18,19] It is also apparent from the work described that the dianion $MeO_2C-N^--SO_3^-$ is a better leaving group than the dithiocarbonate dianion S^--CSO^- and it is suggested that when a *syn*-dehydration is required, the choice of reagent will depend on the ease of carbenium ion formation from the substrate.

Experimental

For general points, see ref. 9.

Diastereoisomers of 1,2-*Diphenyl*-1-(p-*methoxyphenyl*)*butan*-1-*ol* (**3**) *and* (**4**).—(*a*) 1-(*p*-Methoxyphenyl)-2-phenylbutan-1-one[9] (9.56 g, 38 mmol) was treated with phenylmagnesium bromide (56 mmol) in ether (60 ml) at reflux for 20 h. The resulting mixture was poured into dilute sulphuric acid (0.5M; 150 ml), the products extracted with ether (120 ml), and the ether solution concentrated to give an oil which crystallised. Recrystallisation from light petroleum (b.p. 40—60 °C; 100 ml) gave the rel-(1R,2S) *tertiary alcohol* (**3**) (10.1 g, 81%), m.p. 92—93 °C (from light petroleum, b.p. 80—100 °C) (Found: C, 83.3; H, 7.3. $C_{23}H_{24}O_2$ requires C, 83.1; H, 7.3%); δ_H ($CDCl_3$; 60 MHz) 0.71 (3 H, t, *J* 7 Hz, CH_3CH_2), 1.80 (2 H, m, CH_3CH_2), 2.38 (1 H, br, OH), 3.60 (1 H, m, EtC*H*), 3.64 (3 H, s, OMe), 6.61 (2 H, d, *J* 9 Hz, Ar*H ortho* to OMe), and 7.0—7.7 (12 H, m, Ar*H*).

(*b*) Similar treatment of 1,2-diphenylbutan-1-one (42.0 g, 126 mmol) with *p*-methoxyphenylmagnesium bromide (190 mmol) in ether (400 ml) gave the rel-(1R,2R) *tertiary alcohol* (**4**) (47.9 g, 77%), m.p. 114—115 °C (from light petroleum, b.p. 80—100 °C); $\nu_{max.}$ (neat, film from dichloromethane) 3 500br (OH stretch), 2 990m, 1 612m, 1 586w, 1 520m—s, 1 500w—m, 1 456w—m, 1 254m—s, 1 184m, 834m, 725m, and 702m—s cm^{-1} (Found: C, 83.25; H, 7.3. $C_{23}H_{24}O_2$ requires C, 83.1; H, 7.3%); δ_H ($CDCl_3$; 60 MHz) 0.72 (3 H, t, *J* 7 Hz, CH_3CH_2), 1.80 (2 H, m, CH_3CH_2), 2.42 (1 H, br, OH), 3.53 (1 H, m, EtC*H*), 3.68 (3 H, s, OMe), 6.82 (2 H, d, *J* 9 Hz, Ar*H ortho* to OMe), 7.03 (5 H, m, Ph), and 7.42 (2 H, d, *J* 9 Hz, Ar*H meta* to OMe).

Acid-catalysed Dehydration of the Tertiary Alcohols (**3**) *and* (**4**).—Dehydration of either tertiary alcohol (**3**) or (**4**) with 1:2 concentrated hydrochloric acid–ethanol at 80 °C for 4 h gave 1,2-diphenyl-1-(*p*-methoxyphenyl)but-1-ene[8] (yields 95 and 99%) as a 2:1 mixture of *Z*-(**6**) and *E*-(**7**) isomers, as determined from the ratio of intensities of signals in the ^1H n.m.r. spectrum at δ 3.58 and 3.73 (OMe) respectively.

(*Z*/*E*)-1-([$^2H_5$]Phenyl)-1-(*p*-methoxyphenyl)-2-phenylbut-1-ene was prepared from 1-(*p*-methoxyphenyl)-2-phenylbutan-1-one and [$^2H_5$]phenylmagnesium bromide, and dehydration of the resulting deuteriated derivative of the tertiary alcohol (**3**) (85% overall yield).

Isomerisation of Tamoxifen (**8**).—(*a*) *By hydrochloric acid.* A solution of (*Z*)-tamoxifen (200 mg) in a mixture of concentrated hydrochloric acid (10 ml), and ethanol (20 ml) was boiled under reflux for 4 h. The cooled solution was partitioned between ether (50 ml) and aqueous sodium hydroxide (3M; 50 ml). The ether solution was dried (Na_2SO_4) and concentrated to give (*Z*)- and (*E*)-tamoxifen (1:1) as determined from the ratio of intensities of signals in the ^1H n.m.r. spectrum at δ 2.71 and 2.32 (NMe_2) respectively, and at δ 3.91 and 4.07 (triplet for OCH_2).

(*b*) via *A carbenium ion.* A solution of (*Z*)- and (*E*)-tamoxifen (200 mg) in chloroform (2 ml) was stirred at 0 °C and treated with fluorosulphonic acid (0.5 ml). After 15 min, the solution was poured into aqueous sodium hydroxide (3M; 50 ml) and extracted with ether (50 ml). The ether solution was dried (Na_2SO_4) and concentrated to give (*Z*)- and (*E*)-tamoxifen (1.4:1).

Stereoselective Preparation of Tamoxifen (**8**) *from the Tertiary Alcohol* (**5**).—A solution of the tertiary alcohol (**5**) {210 mg; prepared from [1-*p*-(2-dimethylaminoethoxy)phenyl]-2-phenylbutan-1-one and phenylmagnesium bromide}, m.p. 119—120 °C (lit.,[1] m.p. 121—122 °C) in ethanol (12 ml) and concentrated hydrochloric acid (2 ml) was heated under reflux for 20 min. Work-up as in the isomerisation (*a*) above gave a (*Z*)- and (*E*)-tamoxifen (2.1:1) (182 mg, 91%).

(Z)-1-[p-(2-*Chloroethoxy*)*phenyl*]-1,2-*diphenylbut*-1-*ene* (**9**).—1-[*p*-(2-Chloroethoxy)phenyl]-2-phenyl-butan-1-one[13] (30.0 g, 99 mmol) reacted with phenylmagnesium bromide [from bromobenzene (23.55 g, 150 mmol) and magnesium (3.6 g, 150 mmol) in ether (150 ml)]. After 20 h at 20 °C, aqueous work-up as described for the preparation of the tertiary alcohol (**3**) gave an oil which was dehydrated by treatment with concentrated hydrochloric acid (20 ml) in ethanol (200 ml) at reflux for 20 min. The mixture was cooled, poured into water (500 ml), and extracted with ether (2 × 200 ml). The ether solutions were concentrated and the residue dissolved in isopropyl alcohol (700 ml) from which crystallised needles of compound (**9**) as the pure (*Z*)-isomer (17.6 g, 49%), m.p. 107—109 °C (lit.,[9] m.p. 107—109 °C). Concentration of the mother liquors gave a mixture of (*Z*)- and (*E*)-isomers (9.24 g). The conversion of compound (**9**) into (*Z*)-tamoxifen has been reported.[9]

Preparation of Methyl S-*Dithiocarbonate Esters from* (**3**) *and* (**4**).—To a stirred solution of the tertiary alcohol (**3**) (794 mg, 2.39 mmol) in tetrahydrofuran (THF) (15 ml) under nitrogen at 22 °C was added a suspension of potassium hydride (488 mg of a 24.6% suspension in oil; 3.0 mmol) in THF (3 ml). After gas evolution had ceased, carbon disulphide (250 mg, 3.3 mmol) was added, followed after 5 min by the addition of iodomethane (400 mg, 2.8 mmol). After 30 min, the excess of potassium hydride was destroyed by the addition of isopropyl alcohol (2 ml), the mixture poured into water (50 ml) and extracted with ether (2 × 20 ml). The combined ether layers were washed with water (30 ml), dried (Na_2SO_4), concentrated, and the residue chromatographed on silica gel (type H; 12 g). Elution with 5% ether in light petroleum (b.p. 40—60 °C) gave 1,2-diphenyl-1-(*p*-methoxyphenyl)but-1-ene (300 mg, 40%) as a mixture of *E*-(**7**) and *Z*-(**6**) isomers (4:1). Elution with 20% ether in light petroleum gave a mixture of the *dithiocarbonate* S-*esters* (**11**) and (**10**) (4:3) (422.5 mg, 40.4%) as a white foam. Similar treatment of the tertiary alcohol (**4**) gave the but-1-ene as a mixture of *Z*-(**6**) and *E*-(**7**) isomers (9:1) and a mixture of dithiocarbonate *S*-esters (**10**) and (**11**) (2:1) from which the major isomer (**10**) crystallised, m.p. 143—145 °C decomp. (from light petroleum, b.p. 80—100 °C); (Found: C, 71.2; H, 6.3; S, 14.8. $C_{25}H_{26}S_2O_2$ requires C, 71.05; H, 6.2; S, 15.2%); $\nu_{max.}$ (neat, film from THF) 2 990m, 1 726w, 1 648m—s (C=O stretch), 1 614m, 1 586w, 1 520m—s, 1 502w—m, 1 456w—m, 1 260m—s, 1 192m, 866s (C–S stretch), 800m, 736m, and 710m—s cm^{-1}; δ_H (250 MHz; $CDCl_3$) 0.69 (3 H, t, *J* 7 Hz, CH_3CH_2), 1.2—1.5 (1 H, m, CH_3CH_2), 1.9—2.1 (1 H, m,

CH_3CH_2), 2.18 (3 H, s, SMe), 3.82 (3 H, s, OMe), 4.18 (br d, *J* 10 Hz, C*H*Et), 6.71 (2 H, br d, *J* 6.9 Hz, ArH), 6.78 (2 H, d, *J* 9.0 Hz, Ar*H ortho* to OMe), 7.02 (2 H, d, *J* 9.0 Hz, Ar*H meta* to OMe), 7.1—7.35 (6 H, m, ArH), and 7.53 (2 H, br d, *J* 7.1 Hz, ArH); *m/z* 314 (M^+ − MeSH–CSO, 100%), 303 (M^+ − PhCHEt, 31), 299 (18), 275 (13), 243 (52), 197 (40), 91 (22), and 60 (21); molecular ion not observed.

The isomer (**11**) gives δ_H (250 MHz, $CDCl_3$) *inter alia* 0.68 (3 H, t, *J* 7 Hz, CH_3CH_2), 2.19 (3 H, s, SMe), 3.81 (3 H, s, OMe), 4.16 (br d, *J* 10 Hz, C*H*Et), 6.81 (2 H, d, *J* 9 Hz, Ar*H ortho* to OMe), and 7.43 (2 H, d, *J* 9 Hz, Ar*H meta* to OMe).

Thermolysis of the Dithiocarbonate (**10**).—A solution of dithiocarbonate *S*-ester (**10**) (51 mg) in xylene (2 ml) was added over 2 min to xylene (15 ml) at reflux. After 45 min, the solution was concentrated and the residue chromatographed on silica to give a 2:1 mixture of the olefins (**6**) and (**7**) (34 mg, 89%).

Stereoselective Dehydration of the Tertiary Alcohols (**3**) *and* (**4**) *using Carbon Disulphide.—Compound* (**3**). To a stirred solution of the tertiary alcohol (**3**) (336 mg, 1.01 mmol) in THF (15 ml) under nitrogen at 20 °C was added potassium hydride (25% suspension in liquid paraffin; 300 mg, 1.88 mmol) followed after 10 min by carbon disulphide (150 mg, 2.0 mmol). The mixture was heated under reflux for 30 min, then cooled in ice, and the excess potassium hydride destroyed by the addition of isopropyl alcohol (2 ml). Work-up and chromatography as described for the above preparation of the dithiocarbonate *S*-esters gave a 12:1 mixture of the *E*-(**7**) and *Z*-(**6**) isomers of the olefin (147 mg, 47%). Recrystallisation of the product from ethanol gave (*E*)-1,2-diphenyl-1-(*p*-methoxyphenyl)but-1-ene, m.p. 104—105 °C (lit.,[5] m.p. 99—103 °C and lit.,[20] 101—103 °C).

Compound (**4**). To a stirred solution of the tertiary alcohol (**4**) (10.0 g, 30.1 mmol) in THF (150 ml) was added sodium hydride (940 mg, 39.1 mmol) and imidazole (100 mg). The mixture was heated under reflux under nitrogen for 2 h, after which carbon disulphide (2.66 g, 35 mmol) was added. After a further 1 h at reflux, the mixture was cooled in ice and the excess of sodium hydride destroyed by the addition of isopropyl alcohol (5 ml). Work-up and chromatography as described for the preparation of the dithiocarbonate *S*-ester (**10**) (10 × scale) gave a 21:1 mixture of the *Z*-(**6**) and *E*-(**7**) isomers of the olefin (3.54 g, 37%). After recrystallisation three times from ethanol pure (*Z*)-1,2-diphenyl-1-(*p*-methoxyphenyl)but-1-ene (**6**) was obtained, m.p. 121—123 °C (lit.[5] m.p. 116—119 °C and lit.[20] 120—122 °C), at least 99.8% (*Z*)-isomer as determined from examination of the OMe resonances in the ^1H n.m.r. spectrum of a concentrated solution of the product in deuteriochloroform.

Dehydration of the Tertiary Alcohols (**3**) *and* (**4**) *using* N,N,N-*Triethylammonio*-N′-*methoxycarbonylsulphamidate* (**12**).—(*a*) *Directly*. A stirred solution of the tertiary alcohol (**3**) (229 mg, 0.69 mmol) and the inner salt (**12**)[21] (500 mg, 2.1 mmol) in benzene (15 ml) was heated at 50 °C. After 1 h, the mixture was washed with water (15 ml), and the benzene solution dried and concentrated. Chromatography of the residue on silica gave the olefins (**6**) and (**7**) (2.8:1) (217 mg, 90%). Similar treatment of the tertiary alcohol (**4**) also gave the olefins (**6**) and (**7**) (94%) (2.8:1 ratio).

(*b*) Via *Initial alkoxide formation*. To a stirred solution of the tertiary alcohol (**3**) (240 mg, 0.72 mmol) in THF (15 ml) under nitrogen at 22 °C was added potassium hydride (25% suspension in liquid paraffin; 300 mg, 1.88 mmol) followed after 10 min by the salt (**12**) (500 mg, 2.1 mmol). After 1.5 h, work-up as described for the preparation of dithiocarbonate *S*-esters and chromatography gave the olefins (**6**) and (**7**) (90%) (1.8:1). Similar treatment of the tertiary alcohol (**4**) also gave the olefins (**6**) and (**7**) (80%) (3.0:1).

Acknowledgements

This investigation was supported by a grant from the Cancer Research Campaign and Medical Research Council. I thank Dr. M. Jarman for helpful discussions and Dr. W. B. Motherwell for his useful comment on the original manuscript.

References

1 M. J. K. Harper, D. N. Richardson, and A. L. Walpole, B.P. 1 013 907/1965.
2 V. C. Jordan, *Breast Cancer Research and Treatment*, 1983, **2**, 73.
3 M. J. K. Harper and A. L. Walpole, *Nature (London)*, 1966, **212**, 87.
4 V. C. Jordan, B. Haldemann, and K. E. Allen, *Endocrinology*, 1981, **108**, 1353.
5 R. B. Miller and M. I. Al-Hassan, *J. Org. Chem.*, 1985, **50**, 2121.
6 P. L. Coe and C. E. Scriven, *J. Chem. Soc., Perkin Trans. 1*, 1986, 475.
7 For examples see: D. J. Collins, J. J. Hobbs, and C. W. Emmens, *J. Med. Chem.*, 1971, **14**, 952; M. R. Schneider, E. von Angerer, H. Schonenberger, R. Th. Michel, and H. P. Fortmeyer, *ibid.*, 1982, **25**, 1070; D. W. Robertson and J. A. Katzenellenbogen, *J. Org. Chem.*, 1982, **47**, 2387.
8 B. J. A. Furr and V. C. Jordan, *Pharmac. Ther.*, 1984, **25**, 127.
9 M. Jarman and R. McCague, *J. Chem. Res.*, 1985, (*M*) 1342.
10 D. J. Cram and K. R. Kopecky, *J. Am. Chem. Soc.*, 1959, **81**, 2748.
11 P. Sohar, G. Schneider, G. Abraham, T. Horvath, and Z. Mehesfalvi, *Acta Chim. Acad. Sci. Hung.*, 1980, **105**, 201.
12 P. G. Precigoux, C. Courseille, G. Geoffre, and M. Hospital, *Acta Crystallogr., Sect. B*, 1979, **35**, 3070.
13 R. McCague, *J. Chem. Res.*, 1986, (*S*) 58; (*M*) 771.
14 K. Harano and T. Taguchi, *Chem. Pharm. Bull.*, 1972, **20**, 2348.
15 K. Harano and T. Taguchi, *Chem. Pharm. Bull.*, 1972, **20**, 2357.
16 K. G. Rutherford, R. M. Ottenbrite, and B. K. Tang, *J. Chem. Soc. C*, 1971, 582.
17 E. M. Burgess, H. R. Penton Jr., and E. A. Taylor, *J. Org. Chem.*, 1973, **38**, 26.
18 P. Crabbe and C. Leon, *J. Org. Chem.*, 1970, **35**, 2594.
19 J. S. O'Grodnick, R. C. Ebersole, T. Wittstruck, and E. Caspi, *J. Org. Chem.*, 1974, **39**, 2124.
20 Imperial Chemical Industries Ltd., F.P. 68713/1969 (*Chem. Abstr.*, 1970, **72**, 90023).
21 E. M. Burgess, H. R. Penton Jr., E. A. Taylor, and W. M. Williams, *Org. Synth.*, 1977, **56**, 40.

Received 16*th April* 1986; *Paper* 6/734