Tetrahedron: Asymmetry Vol. 1, No. 2, pp. 97-110, 1990
Printed in Great Britain

0957-4166/90 $3.00+.00
Pergamon Press plc

AN ANALOGUE OF THE ANTIOESTROGEN TAMOXIFEN OF SUFFICIENT RIGIDITY TO EXIST AS DISTINCT ENANTIOMERS: SYNTHESIS AND CONFORMATIONAL DYNAMICS STUDIES

RAYMOND McCAGUE

Drug Development Section, Institute of Cancer Research,
Sutton, Surrey, SM2 5NG, U.K.

(*Received* 8 *December* 1989)

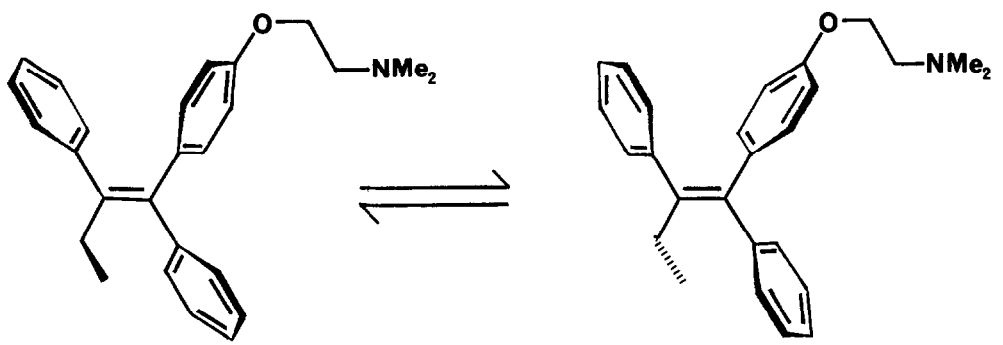
Abstract: The conformationally constrained tamoxifen analogue 1-methyl-8-phenyl-9-[4-[2-(dimethylamino)ethoxy]phenyl]-6,7-dihydro-5H-benzocycloheptene has been synthesised. A key synthetic step is a novel method for introduction of a methyl group into the aromatic ring of benzosuberone by enolate oxygen directed lithiation. Conformational studies were carried out on the methoxy precursor of the above compound. Dynamic ^1H NMR revealed a free energy barrier to racemisation of enantiomeric atropisomers, $\Delta G^{\ddagger}$ = 20 (±1) kcal mol^{-1}. It could be separated by chromatography at -5°C on (+)-poly(triphenylmethylmethacryate) into enantiomers which racemised with $t_{\frac{1}{2}}$ 1.8 h at -5.2°C corresponding to $\Delta G^{\ddagger}$ = 20.9 kcal mol^{-1}. The difficulties in designing analogues having a greater degree of conformational constraint are discussed.

INTRODUCTION

Tamoxifen [ICI-Novadex, (1)] is a drug in clinical use for the treatment of hormone dependent breast cancer[1] whose principal mechanism of action is thought to be displacement of the growth promoting hormone oestradiol from its protein receptor,[2] although recently several other targets for its action have been identified which may contribute to the overall activity.[3] Tamoxifen exists as a pair of enantiomeric atropisomers (**1a**) and (**1b**) which differ in the wind of the helix created by the propeller

like arrangement of the aromatic rings and these rapidly interconvert. Thus its ^1H n.m.r. spectrum at -75°C shows no evidence of the individual chiral forms.[4] A study of the threshold barriers to rotation in the triarylvinyl propellor has been made by Biali and Rappoport who find in the cases of trimesitylethene[5] and trimesitylethenol[6] minimum energy pathways to racemisation (ΔG = 16.8 and 18.4 kcal mol^{-1} respectively) where the two rings in a *cis* relationship or all three rings rotate together to become perpendicular to the olefinic bond in the transition state. Such a mechanism is presumably also the case with tamoxifen although the energy barrier is much lower.

The aim of the present study has been to prepare an analogue of tamoxifen into which has been introduced sufficient rigidity to allow isolation of individual enantiomeric atropisomers for biological studies. Such individual enantiomers would be useful to identify which of the two conformers of tamoxifen is responsible for the biological activity, both in binding to the oestrogen receptor and to other possible targets. This information would be valuable in molecular modelling studies that compare the triarylethylene antioestrogens with the natural hormone to define the topology of the oestrogen receptor binding site.

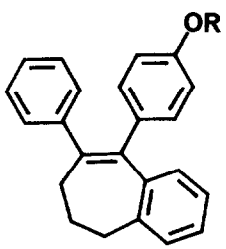


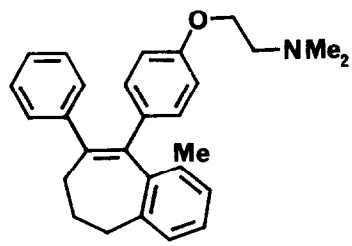
1a **1b**

In designing a suitably constrained tamoxifen analogue, it was considered that structural departure from tamoxifen should be minimised or else any biological results on the products would have little relevance. Our studies on analogues of tamoxifen not isomerisable between E and Z geometric isomers led to the diarylbenzocycloheptene (2). X-Ray crystallographic comparisons of its methoxy precursor (3) with the analogous precursor of tamoxifen showed close structural similarity, especially with respect to the orientations of the phenyl rings. Moreover, the benzocycloheptene (2) had virtually identical *in vitro* biological activity to tamoxifen[4] but distinct atropisomers were distinguishable on the n.m.r. time-scale at -70°C ($\Delta G^{\dagger}$ for inversion ca. 10 kcal mol^{-1})[4] - leading to the choice of the benzocycloheptene as a basis for the introduction of further rigidity. Obviously, the fused phenyl ring is prevented from rotating completely out of plane of the olefinic bond, and a presumed mechanism for conformer inversion is by

flipping of the two remaining rings as depicted in Figure 1. Replacement of the hydrogen indicated (which must pass by the 9-phenyl ring in the transition state) by a larger species should increase the energy barrier.

In this paper is reported the synthesis of the methyl-substituted diarylbenzocycoheptene (4) together with conformational dynamics studies.



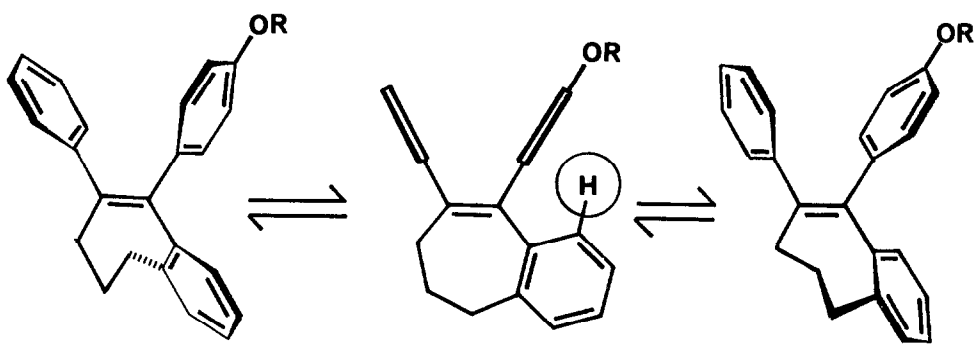


2 R = $CH_2CH_2NMe_2$

3 R = CH_3

4

FIGURE 1 Presumed mechanism for racemisation in the diarylbenzocycloheptene derivatives.



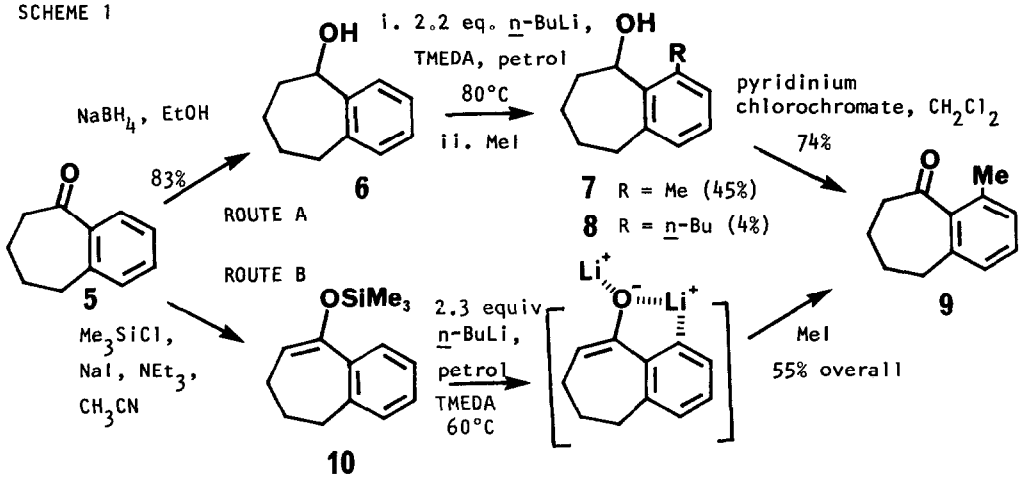
RESULTS AND DISCUSSION

The Preparation of 9-Methyl-1-benzosuberone. The reported synthesis[4] of the benzocycloheptene (2) used 1-benzosuberone as the starting material. The intention of following the same route to synthesise the methyl substituted derivative (4) as used for (2) meant that 9-methyl-1-benzosuberone was required. The known synthesis of this compound described by Caubere *et al*[7] involves trapping of the benzyne intermediate generated by sodium amide treatment of 2-bromotoluene with the enolate of cyclopentanone. Owing to the absence of regiochemical selectivity of coupling to the benzyne, this reaction leads also to the 6-methyl isomer, decreasing the yield and introducing a separation problem. In order to prepare the required isomer specifically, it was chosen

to introduce the methyl group into the 9-position of benzosuberone by means of ring lithiation directed by the oxygen atom. A precident for this approach is the finding by Meyer and Seebach[8] that α-tetralol can be converted into a dianion and alkylated on the ring adjacent to oxygen. Accordingly (Scheme 1, Route A), benzosuberone (5) was reduced and the alcohol (6) treated with n-butyllithium in the presence of TMEDA at 50°. Quenching with iodomethane and work-up afforded the required methylated product (7) (45%), unreacted benzosuberol (39%), and the butylated product (8) (4%), the latter presumably having formed by the rapid exchange between the added iodomethane and unreacted butyllithium. Oxidation of compound (7) with pyridinium chlorochromate then gave the required 9-methyl-1-benzosuberone (9), the overall yield from benzosuberone for this three-step process being 29%.

In an effort to develop a more direct introduction of the methyl group, it was considered that the oxygen atom in the enolate of benzosuberone should be a suitable directing group for ring-lithiation. This approach necessitated the enolate to be generated under conditions compatable with the ring lithiation. A petroleum solution of the lithium enolate (Scheme 1, Route B) could be generated by cleavage of the trimethylsilyl ether (10) with n-butyllithium. After addition of a further equivalent of

SCHEME 1

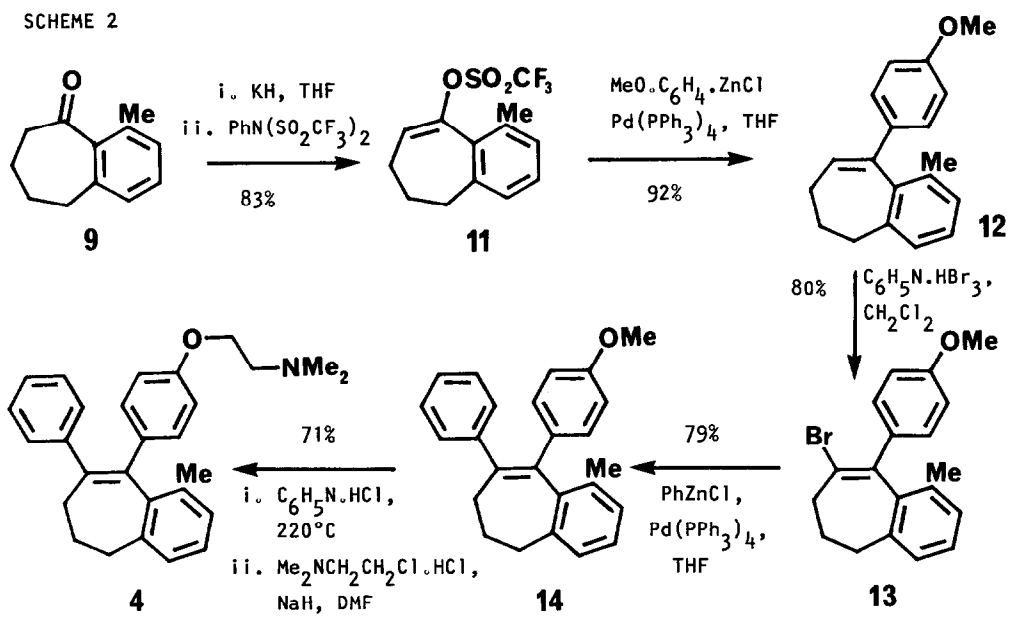


this base and then quenching with iodomethane, the required methylbenzosuberone (9) was obtained directly in 54% yield from benzosuberone. No products methylated α to the carbonyl group were observed.

Some additional experiments were carried out in order to determine the scope of this two-step methylation procedure but reveal its limitations. Alkylation with iodoethane gave only 8% yield and 2-iodopropane gave none of the required product, so dehydroiodination was presumably then the principal reaction. Conversion of tetralone into 8-methyltetralone took place in lower yield (24%) and indanone gave only α-methylated products. Presumably the decreasing ring size draws the enolate oxygen away from the site to be lithiated disfavouring dianion formation.

Conversion of 9-Methyl-1-benzosuberone into the Target Diarylbenzocycloheptene. Although benzosuberone reacts with 4-methoxyphenyl magnesium bromide to give, after dehydration, the arylbenzocycloheptene in 60% yield,[9] similar treatment of the methylbenzosuberone (9), in which approach to the carbonyl function is impeded by the methyl group, gave only enolate formation. The solution to this problem (Scheme 2) is to prepare the enol triflate (11) and displace the triflate function with the aryl zinc chloride under catalysis by tetrakis(triphenylphosphine)palladium (0).* This synthetic method proceeds in good yield (overall 76%).

SCHEME 2



The remainder of the synthesis followed that used to prepare the parent benzocycloheptene analogue (2) of tamoxifen.[4] Thus, electrophilic bromination of the olefin (12) with pyridine hydrobromide perbromide followed by coupling with phenyl zinc chloride under palladium complex catalysis gave the required structural framework (14). The methoxy function was cleaved by heating with pyridine hydrochloride and the resulting phenol alkylated with dimethylaminoethyl chloride to give (4).

Conformational Dynamics Studies and Isomer Separation of (14). With the view that the basic side chain in (4) is unlikely to influence conformational dynamics of the benzocycloheptene framework, studies were carried out on the more readily available methoxy precursor (14). Its ^{1}H n.m.r. spectrum at ambient temperature shows chemical

Footnote *A report on this part of the study has been published - reference 10.

non-equivalence of the geminally related methylene protons on the cycloheptene ring. In particular, the protons at C-5 give distinctly separate multiplets (δ 2.7 and δ 2.9). Therefore, at ambient temperature, the enantiomers do not interconvert on the n.m.r. time scale. At elevated temperatures (Figure 2) the signals broaden and coalesce at 137°C which from the Eyring equation corresponds to $\Delta G^{\ddagger}$ = 20.5 kcal mol^{-1} for the racemisation and an energy barrier of this magnitude should allow the separation of enantiomers at around 0°C.

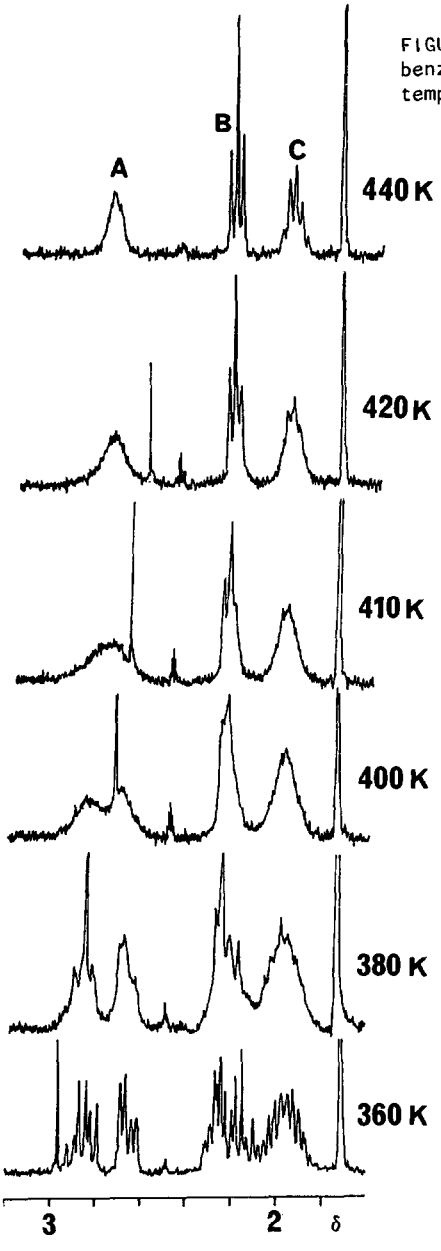
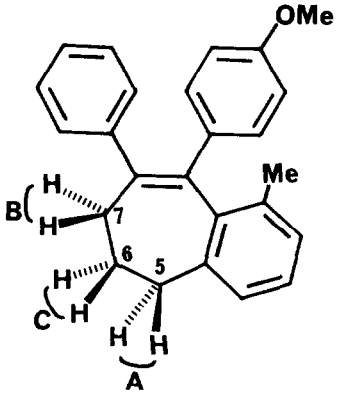


FIGURE 2 ^{1}H NMR spectra of the benzocycloheptene (14) at elevated temperatures in d_6-Me_2SO at 250 MHz.



Okamoto *et al* have demonstrated the efficient separation of enantiomeric conformers differing by the helicity generated by the orientations of aromatic rings, e.g. 1,1'-binaphthol by analytical h.p.l.c. on a column of poly-(+)-(triphenylmethyl-methacrylate).[11] This same system separated the enantiomers of compound (11) completely at -5°C but the isolated enantiomers rapidly racemised if allowed to warm to ambient temperature. The kinetic parameters for the racemisation were established by using the h.p.l.c. used for the separation as an assay for enantiomer proportion. Both isomers were allowed to racemise at -5.2°C. Graphs of the logarithm of the difference in isomer proportion against time were linear and from the gradients, were calculated for either isomer the free energy of activation, $\Delta G^{\ddagger}$ = 20.9 (± 0.1) kcal mol^{-1}. One of the isomers was allowed to racemise at 16.5°C giving $\Delta G^{\ddagger}$ = 21.0 (± 0.1) kcal mol^{-1}.
Taking into account also the result from the dynamic n.m.r. study, it is seen that there is little change in $\Delta G^{\ddagger}$ with temperature such that the magnitude of the activation entropy is less than 5 J $mol^{-1}K^{-1}$. This small value implies the absence of polar character in the transition state as well as the substrates, as expected.

Obviously, the conditions needed for the conversion of the enantiomers of (14) into (4) are far too harsh to allow enantiomeric integrity to be maintained, and unfortunately, attempted separation of the isomers of the dimethylamino derivative (4) were not successful since retention on the column was too strong.

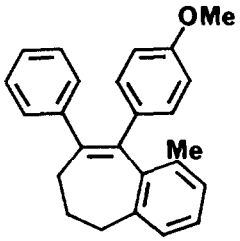
General Discussion and Other Studies. The estimated time for a pure enantiomer of (14) to reach a 3:1 mixture at physiological temperature (37°C) is 28 seconds. Clearly biological experiments cannot be carried out this quickly. It may however be possible to determine binding to the oestrogen receptor since such assays can be carried out at 0°C[12] and possibly lower. Regarding the introduction of greater rigidity, there is the difficulty that further departure from the structure of tamoxifen may destroy receptor affinity. A binding affinity determination on (4) (measured at 20°C) gave a value one-tenth that of tamoxifen and therefore the methyl group impedes receptor binding. Larger alkyl groups may decrease the affinity for the receptor to an imperceptible degree.

In the encumbered 9-arylbenzocycloheptene (15) (see Figure 2), prepared in the same way as (12) using 2,6-dimethyl-4-methoxyphenyl zinc chloride, the extra methyl groups lower the energy barrier to racemisation since the C-5 protons in the n.m.r. spectrum coalesce at -8°C whereas in (12) they coalescence at 57°C. In compound (15) the methoxy bearing ring also suffers hindered rotation and the barrier against chemical equivalance of its diastereotopic aryl-hydrogen atoms is estimated at 13.1 kcal mol^{-1}. This is the same barrier as for racemisation and therefore their equivalence becomes due to enantiomer inversion rather than to rotation of this ring, the molecule having 'gear meshed' methyl groups. Thus the extra methyl groups bring the unfused ring out of plane with the olefinic bond, more readily allowing passage to the transition state of racemisation analogous to that in Figure 1. A further consequence of the unfused ring being brought out of plane is that this ring no longer activates the olefinic bond to electrophilic attack, and attempted electrophilic bromination of compound (15) was

unsucessful. Therefore introduction of methyl groups into the methoxy bearing ring does not provide an approach to more constrained derivatives.

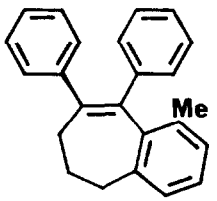
With regard to the supposed transition state (Figure 1) for the racemisation of (14) it is noteworthy that evidence has been reported for a favourable interaction between an aryl ring π-face and a methyl group in methylenehydantoins. Such an interaction could lower the energy of the transition state for racemisation. The literature report had implied that such an interaction would be assisted by electron releasing substituents, in particular alkoxy substituents in the aromatic ring. In order to test whether the methoxy group in (14) was assisting racemisation, the hydrocarbon (16) was prepared by the route used to prepare (14). Dynamic n.m.r. studies however revealed it to have an identical energy barrier to racemisation as (14) so that no evidence for an aryl π-face-methyl interaction could be identified from this study. The energy barriers to racemisation in the four compounds studied by dynamic n.m.r. are summarised in Figure 3.

FIGURE 3 Free energy barriers to racemisation in substituted benzocycloheptene derivatives determined by dynamic NMR spectroscopy.



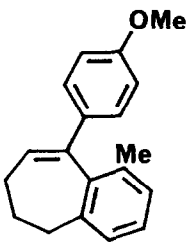
14

20.5 kcal mol^{-1}



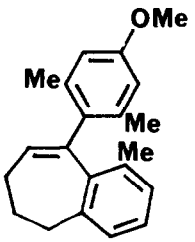
16

20.5 kcal mol^{-1}



12

16.9 kcal mol^{-1}



15

13.2 kcal mol^{-1}

In conclusion, a conformationally restricted analogue of tamoxifen has been prepared but the degree of rigidity will only be sufficient for biochemical studies on individual enantiomer to be carried out below 0°. The design of such studies and the separation of the enantiomers of the amine (4) remain experimental challenges.

EXPERIMENTAL

Proton n.m.r. spectra (250 MHz) in the solvent indicated were recorded on a Bruker AC250 spectrometer fitted with a variable temperature accessory. Infrared spectra were recorded on a Perkin-Elmer 1310 spectrophotometer and mass spectra (electron impact, 70 eV) were obtained with a VG7070 H spectrometer and VG2235 data system. Chromatography refers to column chromatography on silica gel (Merck 15111) with the solvent indicated applied at a positive pressure of 0.5 atm. Melting points were measured on a Koffler hot stage and are uncorrected.

Ring Methylation via Reduction to the Benzosuberol: 9-Methyl-1-benzosuberone (9) (Route A). - To a stirred solution of 1-benzosuberone (24.5 g, 0.153 mol) in ethanol (250 ml) at 20°C was added sodium borohydride (6.5 g, 0.17 mol) in 0.5 g portions over 20 min. The mixture was then poured into water (600 ml), the precipitate collected and recrystallised from 50% aqueous ethanol to give 1-benzosuberol (6) (21.7 g, 87%).

To a stirred solution of this alcohol (20.8 g, 0.128 mol) in light petroleum (b.p. 80-100°C; 180 ml) and N,N,N',N'-tetramethylethylenediamine (32.8 g, 0.282 mol) under nitrogen and cooled by an external water bath at ambient temperature was added a solution of *n*-butyllithium in hexanes (1.5 M; 188 ml, 0.282 mol) over 10 min. The resulting solution was then heated to a gentle reflux whereupon the mixture became deep yellow (dianion) and gas was evolved (n-butane). After 2 h the mixture was cooled to ambient temperature and a solution of iodomethane (36.4 g, 0.256 mol) in light petroleum (b.p. 80-100°C; 100 ml) added over 2 min. The resulting milky white mixture was poured into water (300 ml) and extracted with ether (2 x 150 ml). The extracts were washed with dilute hydrochloric acid (2 x 150 ml), dried (Na_2SO_4) and concentrated. Chromatography of the residue gave, on elution with 10:1 light petroleum (b.p. 60-80°C)-ether: (i) 9-(*n*-butyl)-1-benzosuberol (8) (1.02 g, 4%), m.p. 79-81°C; δ_H ($CDCl_3$) 1.19 (3H, t, J = 7.6 Hz, CH_3), 1.28-1.48 (1H, m) 1.50-1.86 (6H, m), 1.92-2.06 (1H, m), 2.08-2.30 (2H, m), 2.56-2.82 (3H, m), 3.37 (1H, t, J = 13 Hz), 5.38 (1H, d, J = 6.3 Hz, H-9), 6.94-7.10 (3H, m, ArH), (ii) 9-methyl-1-benzosuberol (7) (10.21 g, 45%), m.p. 66-67°C. Found C, 81.75; H, 9.2. $C_{12}H_{16}O$ requires C, 81.8; H, 9.15%. ν_{max} (film) 1685 cm^{-1} (C=O str.); δ_H ($CDCl_3$) 1.42 (1H, q, J = 13 Hz), 1.56-1.92 (3H, m), 1.88-2.04 (1H, m), 2.06-2.28 (1H, m), 2.38 (3H, s, ArMe), 2.62 (1H, dd, J = 6.7, 14.0 Hz), 3.34 (1H, t, J = 12.5 Hz), 5.37 (1H, br. d., J = 6.4 Hz, CHOH), 6.92-7.08 (3H, m, ArH) and (iii) starting 1-benzosuberol (6) (8.05 g, 39%).

To a stirred solution of the 9-methyl-1-benzosuberol (8.11 g, 46 mmol) in dichloromethane (120 ml) at 20°C was added pyridinium chlorochromate (10.4g, 48 mmol) over 10 min. After a further 2 h, the mixture was diluted with an equal volume of ether and filtered through Celite. The filtrate was concentrated. Chromatography of the residue gave, on elution with 3:7 dichloromethane-light petroleum (b.p. 60-80°C), 9-methyl-1-benzosuberone (9) which was purified by distillation, b.p. 110°C at 4.5 mm Hg, and was a colourless oil (5.95 g; 74%), Found C, 82.5; H, 8.1% (Calc. for $C_{10}H_{14}O$: C,

82.7, H, 8.1%).

Ring Methylation *via* the Trimethylsilyl enol ether: 9-Methyl-1-benzosuberone (Route B). - To a stirred solution of sodium iodide (15.3 g, 102 mmol) in acetonitrile (150 ml) was added triethylamine (14.2 ml, 101 mmol), 1-benzosuberone (14.2 g, 88 mmol) and finally chlorotrimethylsilane (12.9 ml, 102 mmol). After 2 h at 20°C the mixture was extracted with light petroleum (b.p. 60-80°C; 2 x 100 ml). The extracts were concentrated to give the trimethylsilyl enol ether (10) (20.3 g, 99%) of sufficient purity for use in the lithiation and methylation. A solution of this enol ether (0.75 g, 3.3 mmol) and N,N,N',N'-tetramethylethylenediamine (1.17 ml, 7.75 mmol) in light petroleum (b.p. 80-100°C; 10 ml) was stirred under nitrogen and a solution of *n*-butyllithium in hexanes (2.5 M; 3.1 ml, 7.75 mmol) was added. The mixture was heated at 60°C for 2 h and then a solution of iodomethane (0.26 ml, 4.2 mmol) in light petroleum (b.p. 80-100°C; 1.5 ml) added in one portion. The mixture was then washed with water (15 ml) and the petrol solution concentrated. Chromatography gave, on elution with 1:20 ether - light petroleum (b.p. 60-80°C), 9-methyl-1-benzosuberone (0.31 g, 55%) identical to a sample produced by Route A, and then unreacted 1-benzosuberone (0.11 g, 21%), the yield of product based on unrecovered starting material being 70%.

Substitution of iodoethane for iodomethane gave 9-ethyl-1-benzosuberone (9%) δ_H ($CDCl_3$) 1.17 (3H, t, $\underline{J}$ = 7.0 Hz, $CH_2C\underline{H}_3$), 1.77-1.81 (4H, m, H-3,4), 2.59-2.77 (6H, m, $C\underline{H}_2CH_3$ and H-2,5), 6.96 (1H, d, $\underline{J}$ = 7.3 Hz), 7.12 (1H, d, $\underline{J}$ = 7.7 Hz), 7.25 (1H, m) and recovered benzosuberone (59%). Upon substitution of 2-iodopropane for iodomethane, t.l.c. showed no alkylated product formed.

Upon substitution of 1-tetralone for 1-benzosuberone, the yield of silyl ether was 96% and after lithiation-methylation, there was obtained 8-methyl-1-tetralone (24%) as an oil, b.p. 90°C at 0.46 mbar (Kugelrohr), Found C, 82.7; H 7.6. $C_{11}H_{12}O$ requires C, 82.5; H 7.6% δ_H ($CDCl_3$) 2.08 (2H, quint, $\underline{J}$ = 6 Hz, H-3), 2.64 (2H, t, $\underline{J}$ = 6.6 Hz and 3H, s, Ar$\underline{Me}$), 2.95 (2H, t, $\underline{J}$ = 6.1 Hz), 7.06-7.34 (3H, m, Ar$\underline{H}$) and recovered starting material (35%).

Upon substitution of 1-indanone for 1-benzosuberone, the yield of silyl ether was 78% but after lithiation-methylation, analysis of the crude product by ^1H n.m.r. spectroscopy showed no 7-methyl-1-indanone or 1-indanone. The principal product was 2-methyl-1-indanone, identified by the doublet signal for the methyl group at δ 1.42.

1-Methyl-9-(trifluoromethanesulphonyloxy)-6,7-dihydro-5$\underline{H}$-benzocycloheptene (11). - A solution of 9-methyl-1-benzosuberone (520 mg, 2.98 mmol) in tetrahydrofuran (1 ml) was added to a stirred suspension of potassium hydride (from 582 mg of a 24.6% suspension in oil, oil removed by washing with light petroleum, 143 mg, 3.58 mmol) in tetrahydrofuran at 20°C under nitrogen. After 15 min, a solution of $\underline{N}$-trifluoromethanesulphonylphenylsulphonimide ($\underline{N}$-phenyltriflimide, 1.072 g, 3.01 mmol) in tetrahydrofuran (4 ml) was added and after a further 10 min, the mixture was partitioned between ether (2 x 15 ml) and water (20 ml). The ether solutions were dried (Na_2SO_4) and concentrated.

Chromatography of the residue, gave on elution with light petroleum, the title compound (756 mg, 83%) as an oil, b.p. 70°C at 0.1 mm Hg (Kugelrohr). Found C, 50.7; H, 4.3; S, 10.4; F, 18.6. $C_{13}H_{13}F_3SO_3$ requires C, 51.0; H, 4.3; S, 10.5; F, 18.6%. ν_{max} 778 (m), 824 (m), 866 (m), 918 (m), 952 (m), 1092 (s), 1160 (vs, S = O sym.str.), 1196 (m), 1366 (s, S = O asym.str.), 2760 (m) and 2845 (m) cm^{-1}; δ_H ($CDCl_3$) 1.8-2.0 (2H, br.), 2.04-2.22 (2H, m), 2.38 (3H, s, Me), 2.64-2.76 (2H, m, H-5), 6.33 (1H, t, J = 7.8 Hz, H-8), 7.07-7.26 (3H, m, ArH).

1-Methyl-9-(4-methoxyphenyl)-6,7-dihydro-5H-benzocycloheptene (12) and other 9-aryl analogues. - A stirred solution of 4-bromoanisole (1.22 g, 6.54 mmol) in tetrahydrofuran (10 ml) under nitrogen at *ca.* -75°C was treated with *tert*-butyllithium (7.3 ml of a 1.8 M solution in hexane; 13.1 mmol) and then with a solution of zinc chloride (891 mg, 6.54 mmol) in tetrahydrofuran (5 ml). The mixture was allowed to warm to ambient temperature and then a solution of the enol triflate (11) (1.0 g, 3.27 mmol) in tetrahydrofuran (5 ml) and tetrakis(triphenylphosphine)palladium(0) (40 mg, 0.03 mmol) were added and the mixture heated under reflux. After 2 h, the mixture was cooled and partitioned between ether (2 x 80 ml) and 0.05 M hydrochloric acid (100 ml). The ether solutions were dried (Na_2SO_4) and concentrated. Chromatography gave, on elution with 1:10 dichloromethane-light petroleum, the title compound (792 mg, 92%), m.p. 95-96°C (from light petroleum, b.p. 80-100°C), Found C, 86.3; H, 7.63. $C_{19}H_{20}O$ requires C, 86.3, H, 7.7%. ν_{max} (neat) 822(m), 1032(m), 1172 (m), 1242 (s), 1288 (m), 1460 (m), 1508 (m), 1604 (m), 2855 (m), 2935 cm^{-1} (m-s); δ_H ($CDCl_3$, recorded at 320 K) 1.65-1.85 (1H, m), 1.82 (3H, s, ArMe), 1.95-2.15 (3H, m), 2.50-2.70 (2H, m), 3.80 (3H, s, OMe), 6.42 (1H, t, J = 7.3 Hz, H-8), 6.81 (2H, d, J = 8.9 Hz, ArH *ortho* to OMe), 7.04-7.20 (5H, m, remaining ArH); δ_H (d_6-Me_2SO, recorded at 400 K) showed *inter alia* 1.84 (br.q. J = 7 Hz, H-7), 2.00 (quint, J = 7 Hz, H-6), 2.56 (t, J = 7 Hz, H-5), m/z 264 (M^+, 100%), 249 ($M-CH_3$, 53%), 236 (36%), 143 (52%).

Other 9-aryl analogues were prepared by substituting the appropriate bromoarene. Thus: bromobenzene afforded 1-methyl-9-phenyl-6,7-dihydro-5H-benzocycloheptene (90% yield), m.p. 69-70°C, Found C, 91.9; H, 7.8. $C_{18}H_{18}$ requires C, 92.3; H, 7.7%. 3-Methyl-4-bromoanisole afforded 1-methyl-9-(2-methyl-4-methoxyphenyl)-6,7-dihydro-5H-benzocycloheptene (89% yield), m.p 107-108°C, Found C, 86.3; H, 8.0. $C_{20}H_{22}O$ requires C, 86.2; H, 8.0% 3,5-Dimethyl-4-bromoanisole afforded 1-methyl-9-(2,6-dimethyl-4-methoxyphenyl)-6,7-dihydro-5H-benzocycloheptene (14) (87% yield), m.p. 127-129°C, Found C, 86.3; H, 8.3. $C_{21}H_{24}O$ requires C, 86.0; H, 8.3%. ν_{max} (neat) 1070 (m), 1140 (m), 1192 (m), 1310 (s), 1446 (m), 1466 (m), 1486 (m), 1602 (m), 2845 (m), 2940 (m-s); δ_H ($CDCl_3$, recorded at 320 K) 1.74 (3H, s, ArMe), 1.75-2.10 (4H, m), 2.01 (6H, br.s, ArMe), 2.60-2.75 (2H, m), 3.78 (3H, s, OMe), 6.21 (1H, t, J = 7.4 Hz, H-8), 6.65 (2H, m, ArH *ortho* to OMe), 6.95-7.15 (3H, m, ArH); δH ($CDCl_3$, recorded at 223 K) showed *inter alia* 2.32 and 2.48 (2 x 3H, s, ArH on OMe bearing ring), 6.44 and 6.54 (2 x 1H, s, ArMe on OMe bearing ring).

1-Methyl-8-bromo-9-(4-methoxyphenyl)-6,7-dihydro-5H-benzocycloheptene (13). - To a solution of the compound (12) (674 mg, 2.55 mmol) in dichloromethane (8 ml) was added pyridine hydrotribromide (1.02 g, 3.19 mmol) and the mixture stirred at ambient temperature. After 2 h, the solution was washed with 2 M hydrochloric acid (10 ml) and 1 M sodium sulphite (10 ml), dried with sodium sulphate and concentrated. Recrystallisation of the residue from light petroleum (b.p. 80-100°C) gave the title compound, (698 mg, 80%), m.p. 87-89°C, Found C, 66.8; H, 5.6; Br, 23.6. $C_{19}H_{19}BrO$ requires C, 66.5; H, 5.6; Br, 23.3%. δ_H ($CDCl_3$) 1.75 (3H, s, ArMe), 1.80-2.05 (1H, m), 2.30-2.55 (3H, m), 2.61 (1H, dd, J = 6, 15 Hz), 2.79 (1H, dt, J = 7, 13 Hz), 3.80 (3H, s, OMe), 6.81 (2H, d, J = 8.7 Hz, ArH *ortho* to OMe), 6.98 (1H, d, J = 7.4 Hz), 7.06 (1H, d, J = 7 Hz), 7.17 (2H, d, J = 8.7 Hz, ArH (ArH *meta* to OMe), 7.1-7.2 (1H, m, ArH).

1-Methyl-8-phenyl-9-(4-methoxyphenyl)-6,7-dihydro-5H-benzocycloheptene (14). - To a stirred solution of phenyl zinc chloride prepared by addition of phenyllithium (1.34 ml of a 2 M solution in 70:30 cyclohexane-ether, 2.7 mmol) to a stirred solution of zinc chloride (368 mg, 2.7 mmol) ether (3 ml) under nitrogen was added a solution of the bromide (308 mg, 0.90 mol) in tetrahydrofuran (6 ml) containing tetrakis(triphenylphosphine)palladium(0) (30 mg) and the mixture heated under reflux. After 5 h, the mixture was cooled and partitioned between ether (30 ml) and water (30 ml). The ether solution was concentrated. Chromatography of the residue on silica (12 g) gave on elution with 1:20 dichloromethane-light petroleum (b.p. 60-80°C) the title compound as a crystalline solid (241 mg, 79%), m.p. 185-187°C (from ethanol), Found C, 88.15; H, 7.25. $C_{25}H_{24}O$ requires C, 88.2; H, 7.1%. δ_H ($CDCl_3$) 1.74 (3H, s, ArMe), 1.85-2.17 (2H, m, H-6), 2.18-2.40 (2H, m, H-7), 2.63 (1H, dd, J = 5,13 Hz, H-5), 2.92 (1H, dt, J = 7, 13 Hz, H-5), 3.71 (3H, s, OMe), 6.56 (2H, d, J = 8.8 Hz, ArH *ortho* to OMe), 6.71 (2H, d, J = 8.8 Hz, ArH *meta* to OMe), 7.03 (1H, d, J = 8 Hz, ArH), 7.05-7.22 (7H, m, ArH); see Figure 1 for elevated temperature n.m.r. spectra in d_6-Me_2SO.

1-Methyl-8,9-diphenyl-6,7-dihydro-5H-benzocycloheptene (16). - Following the above procedure for conversion of compound (9) into (10) and on to (11), 1-methyl-9-phenyl-6,7-dihydro-5H-benzocycloheptene was brominated in 55% yield and the phenyl group introduced in 97% yield to give the title compound as needles, m.p. 150-152°C (from ethanol), Found C, 92.9; H 7.3. $C_{24}H_{22}$ requires C, 92.9; H, 7.1%. δ_H (d_6-Me_2SO, recorded at 320 K) 1.66 (3H, s, ArMe), 1.92-2.08 (2H, m, H-6), 2.10-2.19 (2H, m, H-7), 2.67 (1H, dd, J = 5,12 Hz, H-5), 2.82 (1H, dt, J = 12, 8 Hz, H-5), 6.70-6.75 (2H, m, 9-Ph), 7.00-7.05 (3H, m, 9-Ph), 7.12-7.23 (5H, m, 8-Ph), 7.36 (1H, m, ArH), 7.45 (1H, m, ArH), 7.65 (1H, m, ArH). At elevated temperatures, the protons for C-5, C-6, C-7 changed in an identical manner to those of compound (14).

1-Methyl-8-phenyl-9-[4-(2-dimethylamino)ethoxy]phenyl-6,7-dihydro-5H-benzocycloheptene (4). - A mixture of the methyl ether (14) (265 mg, 0.78 mmol) and pyridine hydrochloride (500 mg, 4.3 mmol) was stirred and heated by means of an oil bath maintained at 210°C.

After 3 h, the mixture was cooled and dissolved in dichloromethane (4 ml). This solution was diluted with ether (20 ml), washed with dilute hydrochloric acid (1 M; 20 ml) and water (20 ml), dried with sodium sulphate and concentrated. The residue was powdered under petrol to give the crude phenol (220 mg, 86%). To a stirred solution of this phenol (64.5 mg, 0.20 mmol) in dimethylformamide (1 ml) under nitrogen was added sodium hydride (30 mg, 1.2 mmol). The mixture was heated to 65°C and 2-(dimethylamino)ethyl chloride (65 mg, 0.45 mmol) was added in portions over 30 min. After 1 hr the mixture was cooled to ambient temperature, isopropanol (0.3 ml) was added to destroy excess sodium hydride and then the mixture partitioned between ether (10 ml) and water (10 ml). The ether solution was dried with sodium sulphate and concentrated. A solution of the residual oil in light petroleum (b.p. 60-80°C) on cooling to -18°C afforded the title compound (56.4 mg, 71%), m.p. 94-96°C, Found C, 84.5; H, 7.9; N, 3.5. $C_{28}H_{31}NO$ requires C, 84.6; H, 7.9; N, 3.5%. δ_H ($CDCl_3$) 1.59 (3H, s, Ar<u>Me</u>), 1.90-2.18 (2H, m), 2.20-2.42 (2H, m), 2.30 (6H, s, $N\underline{Me}_2$), 2.58-2.68 (1H, m), 2.67 (2H, t, <u>J</u> = 5.8 Hz, $OCH_2\underline{CH}_2N$), 2.90 (1H, dt, <u>J</u> = 7.5,13 Hz, H-5), 3.95 (2H, t, <u>J</u> = 5.8 Hz, $O\underline{CH}_2CH_2N$), 6.58 (2H, d, <u>J</u> = 9.0 Hz, Ar<u>H</u> *ortho* to OCH_2), 6.69 (2H, d, Ar<u>H</u> *meta* to OCH_2), 7.02 (1H, d, <u>J</u> = 8 Hz, Ar<u>H</u>), 7.07-7.26 (7H, m, remaining Ar<u>H</u>).

Separation of enantiomers of compound (14) on hplc and kinetics of its racemisation. - A 25 cm x 0.46 cm i.d. analytical column of silica gel [Chiralpak/OT(+) - Daicel Chemical Industries Ltd] was used, cooled by a jacket containing circulating 1:1 ethanol-water supply at -5.2°C. Using a Walters Associates Liquid Chromatograph, elution was with 2-propanol:hexane 10:90 at a flow rate of 0.5 ml min^{-1} and detection by U.V. at 254 nm. A solution of compound (11) (10 μl of 0.9 mg/ml in methanol) was injected. The individual enantiomers gave retention times of 7.75 and 10.3 min. These were collected in a second run directly from the outlet of the column into cardice cooled vials. Enantiomeric purity obtained was 96% as determined by reinjection of 100 μl of the solutions obtained with the injection port cooled by cardice and the syringe cooled to -18°C before use. Kinetics of racemisation were determined by maintaining proportions of the enantiomer solution in a bath at -5.2 or + 16.5°C and assay by hplc as above. Comparison of peak heights gave a better measure of enantiomer proportion than areas once the height of the more retained enantiomer peak was multiplied by 2.42 to compensate for the greater peak width. The following were obtained for the fraction of isomer formed in the racemisation. For isomerisation of the less retained band at -2.5°C: 0 min = 0.025, 25 min = 0.095, 74 min = 0.211, 152 min = 0.323. More retained band at -5.2°C: 0 min = 0.043, 46 min = 0.157, 117 min = 0.276, 180 min = 0.352. More retained band at + 16.5°C: 0 min = 0.043, 1 min = 0.073, 2.5 min = 0.164, 4.5 min = 0.211, 7 min = 0.286, 10 min = 0.349. Graphs of the logarithm of the difference in isomer proportion against time were drawn to determine the rate constant (equal to minus half the gradient) and the free energy of activation according to the equation $k = \frac{RT}{Nh} \exp\left(\frac{-\Delta G^{\ddagger}}{RT}\right)$.

Acknowledgements

I am grateful to Mr. L. Griggs (Institute of Cancer Research) for technical assistance with the hplc separation of atropisomers and to Dr. G. Leclercq (Institut Jules Bordet, Brussels) for the receptor binding affinity determination on the tamoxifen analogue. This study was funded by a grant to the Institute of Cancer Research (Royal Cancer Hospital) from the Cancer Research Campaign and Medical Research Council.

REFERENCES

1. Furr, B.J.A.; Jordan, V.C. *Pharmacol. Ther.* **1984**, *25*, 127.

2. Nicholson, R.I.; Daniel, P.; Gaskell, S.J.; Syne, J.S.; Davies, P.; Griffiths, K. *Antihormones* **1979**, 253.

3. See for example Lam, H.Y.P. *Biochem. Biophys. Res. Commun.* **1984**, *118*, 27; O'Brian, C.A.; Liskamp, R.M.; Solomon, D.H.; Weinstein, I.B. *Cancer Res.* **1985**, *45*, 2462; Brandes, L.J.; Bogdanovic, R.P.; Cawker, M.D.; Bose, R. *Cancer Chemother. Pharmacol.* **1986**, *18*, 21.

4. McCague, R.; Kuroda, R.; Leclercq, G.; Stoessel, S. *J. Med. Chem.* **1986**, *29*, 2053.

5. Biali, S.E.; Rappoport, Z. *J. Org. Chem. Soc.* **1986**, *51*, 2245.

6. Biali, S.E.; Rappoport, Z. *J. Am. Chem. Soc.* **1984**, *106*, 477.

7. Caubere, P.; Guillaumet, G.; Mourad, M.S. *Bull. Chem. Soc. Fr.* **1973**, 3493.

8. Meyer, N.; Seebach, D. *Chem. Ber.*, **1980**, *113*, 1304.

9. Dubois, J.E.; Hegarty, A.F. *J. Chem. Soc. B* **1969**, 638.

10. McCague, R. *Tetrahedron Lett.* **1987**, *28*, 701.

11. Okamoto, Y.; Hatada, K. *J. Liq. Chromatogr.* **1986**, *9*, 369.

12. Wakeling, A.E.; Slater, S.R. *Cancer Treat. Rep.* **1980**, 64, 741.

13. Tan, S.-F.; Ang, K.-P., How, G.-F. *J. Chem. Soc. Perkin Trans 1*, **1988**, 2045.