The Role of the 2-Methyl Substituent in Governing Stereoselective Formation of the *E* Isomer in the Synthesis of 4-Hydroxy-2-methyltamoxifen (1-{4-[2-(Dimethylamino)ethoxy]phenyl}-1-(4-hydroxy-2-methylphenyl)-2-phenylbut-1-ene)

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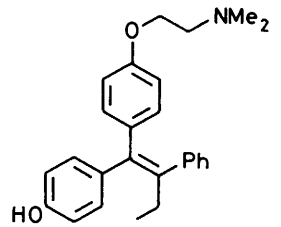
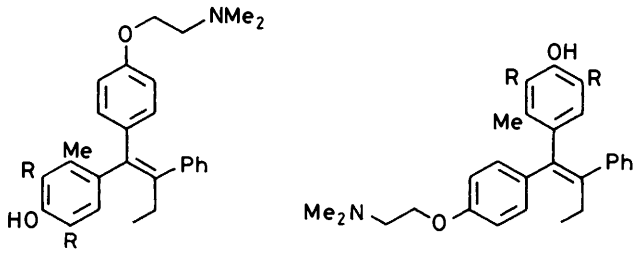
Syntheses of 4-hydroxy-2-methyltamoxifen (1-{4-[2-(dimethylamino)ethoxy]phenyl}-1-(4-hydroxy-2-methylphenyl)-2-phenylbut-1-ene) by dehydration of diastereoisomeric triphenylbutan-1-ol precursors were compared. Crystal structures of these diastereoisomers have now both been determined. Acid treatment of either diastereoisomer gave predominantly the *E* olefin (8:1 *trans–cis*), consistent with a mechanism proceeding by way of a common carbenium ion intermediate whereby the 2-methyl group destabilises the transition state that would lead to *Z*-olefin. A synthesis of 4-hydroxy-2,3,5-trimethyltamoxifen proceeded similarly. The (*E*)-4-hydroxy-2-methyltamoxifen was more resistant to isomerisation into a *Z–E* mixture than was 4-hydroxytamoxifen but a 3:1 *trans–cis* equilibrium mixture could be obtained. The 4-hydroxy-2,3,5-trimethyltamoxifen gave the same ratio of isomers at equilibrium as did the 4-hydroxy-2-methyl compound but it isomerised at a faster rate. It was shown from the ^{1}H n.m.r. spectrum of the carbenium ion derived by trifluoromethanesulphonic acid treatment of the model compound 1-(4-methoxy-2-methylphenyl)-1-(4-methoxyphenyl)-2-phenylbut-1-ene that, in these systems, the aryl ring that is best able to stabilise the positively charged carbon atom is preferred *cis* to the 2-phenyl ring in the alkene product.

4-Hydroxytamoxifen (1-{4-[2-(dimethylamino)ethoxy]-phenyl}-1-(4-hydroxyphenyl)-2-phenylbut-1-ene) (**1**) is a metabolite of the antioestrogenic drug tamoxifen in patients undergoing treatment for hormone-dependent breast cancer,[1] and it has much greater antioestrogenic potency than the parent drug.[2,3] Two of the problems associated with biochemical evaluation of 4-hydroxytamoxifen are the need to prepare the pure *trans*† isomer and to ensure that its isomerisation does not take place under the test conditions used. The required antioestrogenic activity is normally associated only with the *trans* isomers of triarylbutenes.[5,6] However, the isomerisation which is a consequence of the conjugation between the central double bond and the hydroxy group is very facile[7,8] and has been shown to occur during cell culture experiments.[9,10]



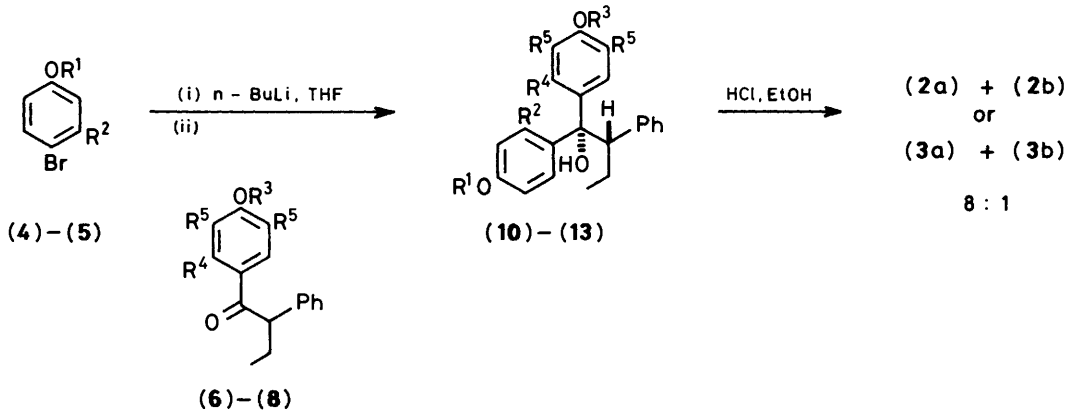
(**1**)



(**2a**) R = H (**2b**)
(**3a**) R = Me (**3b**)

We have reported that 4-hydroxy-2-methyltamoxifen has similar biological activity to 4-hydroxytamoxifen but the synthesis had given only the required *E-trans*-isomer (**2a**).[4] More importantly this compound was resistant to isomerisation into an *E–Z* mixture.[4] These results were thought unlikely to be a consequence of a much greater thermodynamic stability of the *E-trans*-isomer since energy calculations predicted the *E* and *Z* isomers to have lowest-energy conformations of similar energy.[11] In this paper, we describe the results of experiments aimed at defining the role of the methyl group both in controlling the stereochemical outcome of the synthesis and in preventing unwanted isomerisation. To this end, 4-hydroxy-2-methyltamoxifen (**2a**, **b**) was prepared by a route proceeding through a tertiary alcohol precursor diastereoisomeric to that used previously.[4] 4-Hydroxy-2,3,5-trimethyltamoxifen (**3a**, **b**) was also prepared (Scheme 1) originally for the purpose of determining the effect of flanking methyl groups on the rate of metabolic conjugation of the hydroxy group. Its synthesis, and studies of the isomerisation of its individual isomers into an *E–Z* mixture, are reported here since the results are relevant to the present investigations.

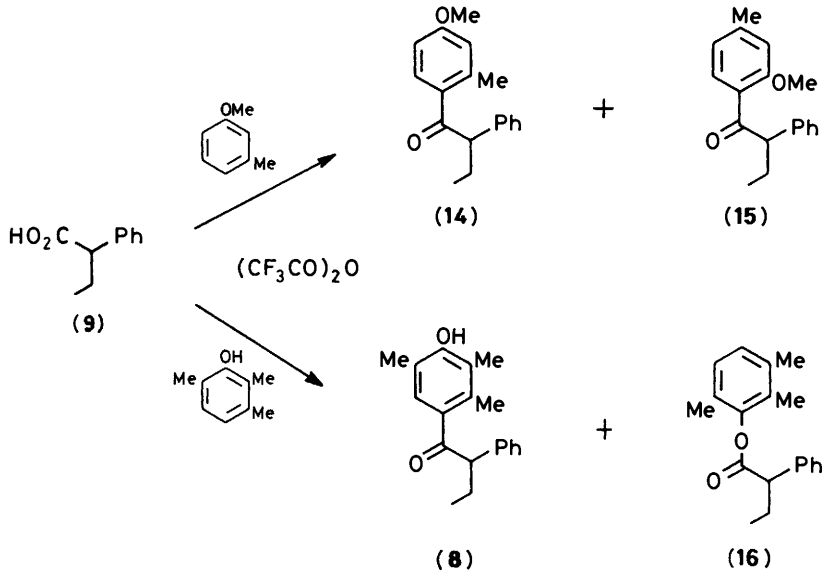
† The descriptors *trans* and *cis* used in this article refer to the relationship of the ring bearing the basic side-chain to the ethyl group. This nomenclature has been used previously.[4]



		R¹	R²	R³	R⁴	R⁵
(4) + (6) →	(10)	THP	Me	$CH_2CH_2NMe_2$	H	H
	(11)	H	Me	$CH_2CH_2NMe_2$	H	H
(5) + (7) →	(12)	$CH_2CH_2NMe_2$	H	H	Me	H
(5) + (8) →	(13)	$CH_2CH_2NMe_2$	H	H	Me	Me

THP = tetrahydropyran - 2-yl

Scheme 1.



Scheme 2.

Results and Discussion

Synthesis of the Triarylbutan-1-ols.—The triarylbutene derivatives were prepared as shown in Scheme 1. The required *ortho*-methyl-substituted ketones were prepared as shown in Scheme 2. Although Friedel–Crafts condensation of anisole with 2-phenylbutanoic acid (**9**) gives acylation exclusively *para* to the methoxy group,[12] the corresponding reaction with 3-methylanisole gave both the required product (**14**) and its isomer (**15**) in a 2.6:1 ratio. Compound (**15**) was formed as a consequence of the *para*-directing influence of, and steric hindrance by, the methyl group. These isomeric ketones were separated by preparative h.p.l.c. and distinguished by ^{1}H n.m.r. using a lanthanide shift reagent. Co-ordination of the shift reagent to the ketone oxygen atoms in (**14**) and (**15**) gave a strong downfield shift of the methyl group protons in the required product (**14**) and of the methoxy group in the unwanted product (**15**). Demethylation of compound (**14**) with pyridine hydrochloride gave the phenol (**7**). The ketone (**8**) was prepared directly by acylation of 2,3,6-trimethylphenol. Despite hindrance by the 2- and 6-methyl groups, the ester (**16**) was the major product. Nevertheless, sufficient of the ketone (**8**) could be isolated easily from the product mixture.

In each of the routes, the aryl-lithium was generated from a bromobenzene derivative [(**4**), (**5**)] prepared by alkylation of the appropriate bromophenol. Reaction of the aryl-lithium with the appropriate ketone [(**6**)—(**8**)] formed in each case a tertiary alcohol. The configuration of the tertiary alcohol (**10**) has been determined, as previously described,[11] as *rel*-(1*R*,2*R*) by *X*-ray crystallography. In order to compare its stereochemistry with that of the tertiary alcohol (**12**) prepared by the complementary route, the tetrahydropyranyl ether function of compound (**10**) was cleaved by mild acid hydrolysis. The resulting phenol (**11**)

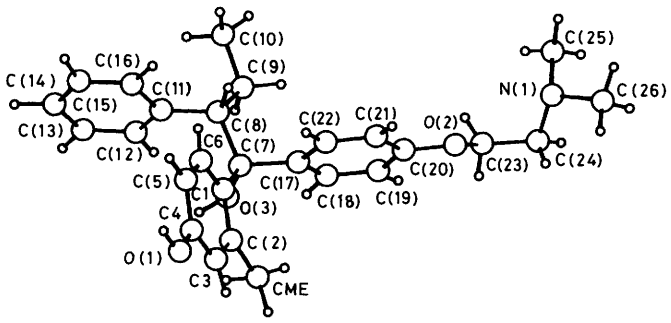


Figure 1. Ball and stick representation of the crystal structure of the tertiary alcohol (**12**) in its 1:1 complex with toluene

Table 1. Comparison of the dihedral angles of aryl rings in compound (**12**) with those in compound (**10**) and in various tamoxifen derivatives[a]

	Dihedral angles (°)			
	Compound (**12**)	Compound (**10**)[11]	Tamoxifen[11]	4-Hydroxy-2-methyl-tamoxifen[11] (**2a**)
Planes 1/2	92.5	48.3	59.0	49.9
Planes 1/3	87.0	91.0	87.0	96.6
Planes 2/3	15.5	55.1	57.0	62.2

[a] Planes defined as : Plane 1: C(1)—C(6); Plane 2: C(11)—C(16); Plane 3: C(17)—C(22). Atoms numbered as in Figure 1.

gave a ^{1}H n.m.r. spectrum different from that of the tertiary alcohol (**12**). Therefore compounds (**11**) and (**12**) are diastereoisomers and hence the configuration of (**12**) is *rel*-(1*R*,2*S*). This assignment was subsequently confirmed by *X*-ray analysis of the crystalline 1:1 complex of (**12**) and toluene. A ball and stick representation of compound (**12**) is illustrated in Figure 1. The configurations of (**11**) and (**12**) are such that the tertiary alcohols had formed in accordance with Cram's rule.[13] This rule is known to be followed in the synthesis of related triphenylbutan-1-ols that do not have the *ortho*-methyl substitution.[14,15] Hence the *ortho*-methyl group in either reactant has no influence on the stereochemistry of the addition reaction.

Favoured Conformations of the Triarylbutan-1-ols.—Crystal structure of (**12**). In the crystal structure of compound (**12**), the molecule adopts a conformation with the C(1) hydroxy group and C(2) hydrogen atom [C(7) and C(8) in Figure 1] in an anti-periplanar orientation; this same relationship was observed in the crystal structure of compound (**10**).[11] Hence the presence of the *ortho*-methyl group not only does not influence the stereochemical course of the addition reaction to the ketones but also does not influence the favoured conformation of the tertiary alcohols with regard to rotation about the C(1)–C(2) bond of the butanol. The molecular structure of compound (**12**) does, however, differ significantly from that of the triarylbutenes (tamoxifen analogues) and the tertiary alcohol (**10**) by having the three phenyl rings oriented differently with respect to one another (Table 1).

^{1}H *N.m.r. spectra.* The ^{1}H n.m.r. spectra of the tertiary alcohols (Table 2) are consistent with the conformation [with respect to rotation about the C(1)–C(2) bond] observed in the crystal, indicating it is also that which is favoured in solution. Thus, it is the ring anti-periplanar to the ethyl group that gives signals for its protons (a—d in Table 2) at relatively low frequency owing to the through space shielding influence of the adjacent vicinal phenyl ring. Such an effect is well catalogued in the 1,1,2-triarylbutene series where there is shielding between rings in a *cis*-relationship.[16–18]

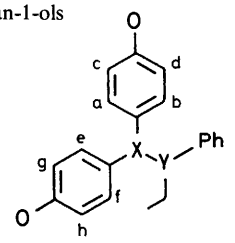
Dehydration of the Triarylbutan-1-ols.—Acid-catalysed dehydration of either diastereoisomeric tertiary alcohol gave the *E*(*trans*) and *Z*(*cis*) alkenes in an 8:1 ratio. The configurations of the components of the mixture were easily assigned from their ^{1}H n.m.r. spectra (Table 2). In common with other 1,1,2-triarylbutenes (and the 1,1,2-triarylbutanols discussed above) the ring *trans* to the ethyl group gives signals for its protons at relatively low frequency. In addition, the OCH_2 protons of the basic side-chains had a chemical shift above δ 4.0 only when the ring bearing this chain was *cis* to the ethyl group.[19]

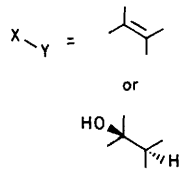
The product composition following the dehydration is consistent with an *E*1 elimination mechanism that proceeds *via* a carbenium ion intermediate which is sufficiently long-lived to form an equilibrium conformation which, of course, is independent of the stereochemistry of the tertiary alcohol. This is comparable to the situation of the dehydration of 1-(4-alkoxyphenyl)-1,2-diphenylbutan-1-ols when the product composition was again independent of the tertiary alcohols, but the ratio of isomeric products was 2:1 *Z*(*trans*):*E*(*cis*).[15]

Equilibration of the E- and Z-Isomers of the Triarylbutenes.—The foregoing studies indicate that the stereochemical preference for the *E*-(*trans*)-isomers is a consequence of the carbenium ion intermediate adopting a preferred conformation, proton loss from which leads to the *E* isomer. However, we could not discount the possibility that this could reflect a much greater thermodynamic stability of the *E* isomer. In order to gain a fuller understanding of the role of the methyl group it was therefore necessary to find the position of equilibrium between the *E* and *Z* isomers of the olefins. It is known that 4-hydroxytamoxifen readily forms a 1:1 *E*–*Z* equilibrium mixture on exposure to radical sources.[7] When either of the 2-methyl-substituted analogues (**2a**) or (**3a**) was mixed with 4-hydroxytamoxifen, and the mixture dissolved in unpurified deuteriochloroform, isomerisation of the 4-hydroxytamoxifen was complete within 1 h but neither (**2a**) nor (**3a**) showed any sign of isomerisation after this time as determined by ^{1}H n.m.r. spectroscopy. In the case of 4-hydroxy-2,3,5-trimethyltamoxifen but not for 4-hydroxy-2-methyltamoxifen, both the *E*- and *Z*-isomers could be isolated pure. Either isomer (**3a**) or (**3b**) gave an equilibrium 3:1 *E*–*Z* mixture after 55 days in deuteriochloroform at room temperature. Equilibration of the *trans*-isomers (**2a**) and (**3a**) was also achieved in warm deuteriochloroform at 47 °C to give in both cases a 3:1 *E*–*Z* mixture. The 4-hydroxy-2,3,5-trimethyltamoxifen (**3a**) isomerised at a slightly faster rate but when a 1:1 mixture of the compounds (**2a**) and (**3a**) was dissolved in deuteriochloroform, the latter was found to isomerise at about twice the rate of the former owing to inhibition of the isomerisation of (**2a**) by (**3a**). This observation is consistent with the isomerisation proceeding by a radical intermediate (see general discussion) and that formed from (**3a**) is the more stable, so that (**3a**) preferentially scavenges the low concentration of available radical sources.

N.m.r. Studies of Independently Generated Carbenium Ions.—It has been shown that a carbenium ion could be generated by treatment of 1-(4-methoxyphenyl)-1,2-diphenylbut-1-ene (**17**) with fluorosulphonic acid and could be studied by ^{1}H n.m.r. spectroscopy.[15] It was hoped similarly to generate a carbenium ion related to the intermediate in the synthesis of 4-hydroxy-2-methyltamoxifen. For this purpose, the model dimethoxy compound (**19**) was synthesised by reaction of 1-(4-methoxyphenyl)-2-phenylbutan-1-one with 2-methyl-4-methoxyphenyl-

Table 2. ^{1}H N.m.r. spectra of triarylbut-1-enes and triarylbutan-1-ols





(2a), (2b), (3a) and (3b)

(12) and (13)

Compound	(2a)	(2b)	(3a)	(3b)	(11)	(12)	(13)
Configuration	*E-trans*	*Z-cis*	*E-trans*	*Z-cis*	(1*R*,2*R*)	(1*R*,2*S*)	(1*R*,2*S*)
Chemical shifts:							
a	6.69	Me	6.76	Me	6.73	Me	Me
b		6.73		6.57		7.39	7.27
c	6.34	6.40	6.52	Me	6.43	6.23	Me
d		6.35		Me		6.35	Me
e	Me	7.09	Me	7.13	Me	7.13	7.06
f	7.07		6.86		7.40		
g	6.63	6.73	Me	6.57	6.46	6.81	6.78
h	6.66		Me		6.66		
$MeCH_2$	2.20—2.40	2.48—2.70	2.20—2.50	2.50—2.75	1.68—2.05	1.40—1.80	1.30—1.80
$MeCH_2$	0.81	0.99	0.80	0.99	0.71	0.64	0.61
$MeCH_2CH$	—	—	—	—	4.05	3.51	3.49
$OCH_2CH_2NMe_2$	2.34	2.35	2.28	2.33	2.14	2.20	2.20
$OCH_2CH_2NMe_2$	2.60—2.82	2.76	2.63	2.72	2.50	2.60	2.60
$OCH_2CH_2NMe_2$	3.92	4.04	3.91	4.05	3.81	4.00	3.91
Ph	7.10—7.24	6.90—7.08	7.08—7.32	7.00—7.25	6.82—7.10	6.95—7.25	7.00—7.22
ArMe	2.02	1.93	2.12	1.94	1.99	1.81	1.74
			2.18	1.97			1.88
			2.25	2.04			2.09
ArOH					9.25	8.94	7.80
t-OH					5.24	5.14	5.10

Spectra were recorded at 250 MHz in $(CD_3)_2SO$ solutions [compounds (**11**)—(**13**)] or in $CDCl_3$ solutions [compounds (**2a**, **b**), and (**3a**, **b**)]. In all cases coupling constants were in the following ranges: a—c, b—d, e—g, f—h: 8.6—9.0 Hz; $MeCH_2$: 7.1—7.4 Hz; $OCH_2CH_2NMe_2$: 5.5—5.8 Hz.

lithium and dehydration of the resulting tertiary alcohol. The product was obtained as the now expected 8:1 mixture of *E* and *Z* isomers and the *E* isomer could be isolated pure by recrystallisation. Treatment of compound (**19**) with fluorosulphonic acid in deuteriochloroform did not yield a stable carbenium ion but when trifluoromethanesulphonic acid was used, the resultant deep red carbenium ion solution was sufficiently stable for study at ambient temperature. Its spectrum revealed that it had been formed as a 6.5:1 mixture of two components; presumably diastereoisomers resulting from a slow rotation of the *ortho*-methyl substituted ring on the n.m.r. time scale. The n.m.r. spectrum of the similarly generated ion (**18**) from (**17**) was analysed for comparison, the data being given in Figure 2.

The signals of the methoxy groups in the model compound (**19**) and the ion (**20**) were assigned by nuclear Overhauser enhancement measurements in which pre-irradiation of the methoxy proton resonances gave enhancement of the adjacent ring protons. In the olefinic compound (**19**), it was the methoxy group in the less substituted ring that gave the lower frequency signal owing to the shielding influence of the adjacent 2-phenyl ring. However in the carbenium ion the signals were reversed, as a result of a δ 0.6 shift to higher frequency of the methoxy group protons of the less substituted ring. The signal for the methoxy group of the trisubstituted ring was shifted by only δ 0.21. These shifts give a measure of the relative contributions that the rings make towards stabilisation of the positive charge, and show that the effect of the *ortho*-methyl group is destabilising. Since the shift of the methoxy group protons on protonation of (**17**) was analogous to that of (**19**), also δ 0.6, the extent of this destabilisation is such as effectively to cancel the stabilising influence of the methoxy group. The highest-frequency resonances in the spectrum of the ion (**20**) are due to the protons in the disubstituted ring adjacent to the positively charged carbon. These signals appear as two distinct doublets presumably due to the hindered rotation about the bond joining this ring to the trivalent carbon. Unexpectedly, the *ortho*-methyl group in the major component of the ion (**20**) is shifted to lower frequency relative to the olefin (**19**). We speculate that this is due to movement of the methyl group further into the shielding zone of the geminal 1-aryl group. A similar effect is observed in the ion (**18**) where, although the protons *meta* to the methoxy group give the highest-frequency signals in the spectrum, the corresponding protons in the 1-phenyl ring give the lowest frequency of all the aromatic proton signals. Signals for the two phenyl rings in the ion (**18**) were distinguished by subtraction of the spectrum of the carbenium ion derived from the [1-$^2H_5$]phenyl analogue.[15]

On quenching of the carbenium ion (**20**) by addition of water, the olefin (**19**) was recovered as a 7:1 mixture of *E* and *Z* isomers, *i.e.* a similar ratio to that obtained by dehydration of the tertiary alcohol precursor.

General Discussion.—Clearly greater specificity towards the *E*-(*trans*)-isomers of the methyl-substituted triarylbutenes is observed after the dehydration than would have been predicted on the basis of the thermodynamic equilibrium ratios. The kinetic product ratio reflects the relative energies of the transition states leading to (*E*) or (*Z*) products which would be expected to resemble the relevant carbenium ion conformation, and it is clear that the methyl group exerts a greater influence in the transition state for the dehydration than it does in the products.

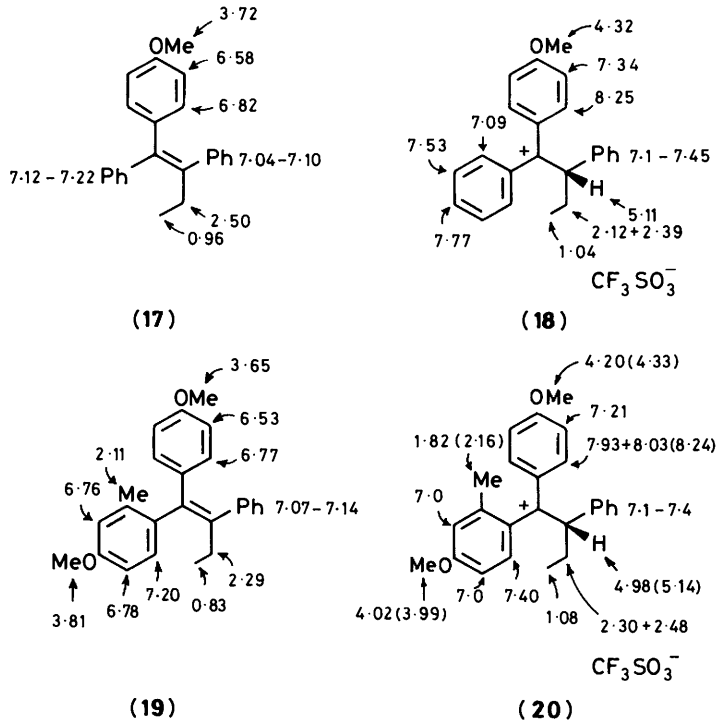


Figure 2. ^1H Chemical shifts ($CDCl_3$) of triarylbutenes (**17**) and (**19**) and the carbenium ions derived by protonation of them with trifluoromethanesulphonic acid. Values in parentheses for (**20**) are for the minor component

It has been established that in the triphenylbutenes the rings adopt stable conformations in which they are rotated *ca.* 50° out of the plane of the central double bond[20,21] such that the methyl group will exert only minimal non-bonded repulsions to adjacent groups. However, assuming that there remains a sufficient repulsive interaction which is greater to a phenyl ring than to an ethyl group, then this will explain the 3:1 preference for the *E*-(*trans*)-isomer at equilibrium. In the carbenium ion, there would be a tendency for the rings attached to the positively charged carbon atom to approach planarity with the potential olefinic bond in order to achieve maximum overlap with the vacant sp^2 orbital. In doing so, the methyl group would be rotated into a position where interactions with adjacent substituents are increased. However, there is an additional explanation for the favoured carbenium ion conformation. Since the trisubstituted methyl-bearing ring is prevented from approaching planarity with the positively charged carbon atom, the disubstituted ring would be expected to provide the greater stabilising contribution and bear the greater partial positive charge. This idea is strongly supported by n.m.r. data on an independently generated carbenium ion in which it is shown that the presence of the *ortho*-methyl group essentially cancels the electron-releasing influence of the *para* substituent in the same ring. A favourable interaction with the vicinal 2-phenyl ring then explains formation of the favoured *trans*-olefin. Such an interaction was invoked to explain the preference for *trans*-olefin from the dehydration of 1-(4-alkoxyphenyl)-1,2-diphenylbutan-1-ols in which the alkoxy-bearing ring would be expected to provide the greater stabilising contribution to the carbenium ion intermediate.[15]

The mechanism for isomerisation in deuteriochloroform, and probably in cell culture, is a radical chain mechanism in which the first step is abstraction of the hydroxy hydrogen atom by a radical source to give a species with reduced bond order in the central linkage as illustrated in Figure 3. This species has bonding resembling that of the carbenium ion intermediate of the dehydration. The *ortho*-methyl group will reduce the likelihood of the hydroxylated ring approaching co-planarity with the double bond, thereby reducing the importance of the resonance form **B** in Figure 3 which gives rise to a reduced bond order in C(1)–C(2) leading to rotation of this bond and isomerisation. In addition, the radical character is restricted to the oxygen and attached phenyl ring, and hence the 2-methyl substitution destabilises the radical and reduces its tendency to form.

The finding that 4-hydroxy-2,3,5-trimethyltamoxifen is more readily isomerised in chloroform than is 4-hydroxy-2-methyltamoxifen is a consequence of the extra pair of methyl groups stabilising the radical intermediate through hyperconjugative electron release. These methyl groups are however in the wrong position to stabilise the carbenium ion and consequently the kinetic product ratio of the dehydration is unchanged. Nevertheless it is noteworthy that the absence of effect of the extra methyl groups on the kinetic product ratio and on equilibrium position indicates that there is no effect resulting from buttressing of the 2-methyl group in 4-hydroxy-2,3,5-trimethyltamoxifen by the 3-methyl group. Thus in 4-hydroxy-2,3,5-trimethyltamoxifen, the rotational entropy of the 2-methyl group is not important but rather its steric bulk is.

These results show how the incorporation of a methyl group can greatly influence the preferred configurational or conformational structure of a drug. Occasions may arise when the introduction of judiciously placed methyl groups in other drugs could be similarly beneficial.

Experimental

Unless a reference is given, starting materials were commercially available. Tetrahydrofuran (THF) was dried by distillation from potassium benzophenone. Preparative high-performance liquid chromatography (h.p.l.c.) was carried out on a Jobin-Yvon Chromatospac Prep 100 instrument. Otherwise chromatography refers to column chromatography on silica gel (type 60) with the solvent indicated applied at a positive pressure

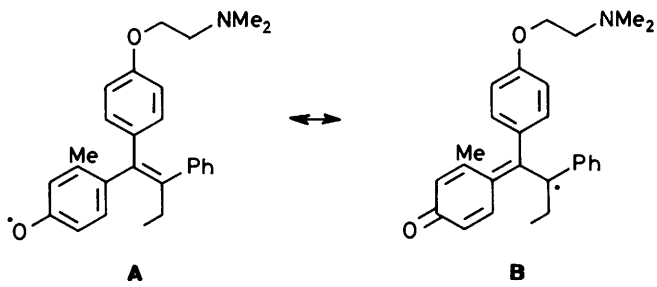


Figure 3. Canonical forms of the intermediate in the free-radical-catalysed isomerisation of 4-hydroxy-2-methyltamoxifen

of 0.5 atm. Routine 60 MHz ^{1}H n.m.r. spectra were obtained using a Perkin-Elmer R12B spectrometer and 250 MHz spectra were obtained on a Bruker AC250 spectrometer. Mass spectra (electron impact, 70 eV) were obtained with a VG7070H spectrometer and VG2235 data system. M.p.s were determined on a Kofler hot-stage and are uncorrected.

4-Hydroxy-2-methyltamoxifen. (Method 1). Details of the synthesis of compounds (**2a**), (**4**), (**6**), and (**10**) have been published.[4]

Hydrolysis of the Tertiary Alcohol (**10**).—A solution of the tetrahydropyranyl ether (**10**) (15.9 g, 32.8 mmol) and adipic acid (12.7 g, 87 mmol) in ethanol (80 ml) and water (80 ml) was heated under reflux for 1 h, then cooled and adjusted to pH 10 by the addition of aqueous sodium hydroxide. The solution was diluted with water (150 ml) and extracted with ether (150 ml). The combined ether layers were washed with saturated brine (15 ml), dried (Na_2SO_4), and concentrated. Chromatography of the residue [dichloromethane–methanol (10:1)] gave rel-(1R,2R)-1-{4-[2-(*dimethylamino*)*ethoxy*]*phenyl*}-(4-*hydroxy*-2-*methylphenyl*)-2-*phenylbutan*-1-*ol* (**11**) (4.03 g, 40%), m.p. 183—185 °C (from methanol) (Found: C, 76.8; H, 8.05; N, 3.1. $C_{27}H_{33}NO_3$ requires C, 77.1; H, 8.15; N, 3.3%).

4-Hydroxy-2-methyltamoxifen. (Method 2). 1-(4-*Hydroxy*-2-*methylphenyl*)-2-*phenylbutan*-1-*one* (**7**).—Trifluoroacetic anhydride (18.9 ml, 0.134 mol) was added dropwise over 15 min into a stirred mixture of 3-methylanisole (20 g, 0.122 mol) and 2-phenylbutanoic acid (20 g, 0.122 mol) at 25—30 °C. After a further 2 h, the mixture was poured into stirred saturated sodium hydrogen carbonate solution (150 ml). When gas evolution had ceased, the mixture was diluted with water (150 ml) and extracted with ether (150 ml, then 3 × 500 ml). The combined extracts were dried with sodium sulphate and concentrated. Chromatography of the residue [light petroleum (b.p. 60—80 °C)–ether (50:1)] gave: (i) 1-(4-methoxy-2-methylphenyl)-2-phenylbutan-1-one (**14**) (18.9 g, 58%) as a viscous oil, b.p. 197—198 °C at 9 mmHg; δ($CDCl_3$; 60 MHz) 0.90 (3 H, t, *J* 6 Hz, $CHCH_2$*Me*), 1.65—2.60 (2 H, m, $CHCH_2$Me), 2.45 (3 H, s, ArMe), 3.73 (3 H, s, ArOMe), 4.32 (1 H, t, *J* 6 Hz, C*H*Et), 6.50—6.85 (2 H, m, ArH *ortho* to OMe), 6.90—7.45 (5 H, m, Ph), and 7.50—7.95 (1 H, m, ArH *meta* to OMe); *m/z* 268 ($M^{+\bullet}$, 0.3%) and 149 (M^+ − PhCHEt, 100). It gave an orange 2,4-*dinitrophenylhydrazone*, m.p. 114—116 °C [from light petroleum (b.p. 40—60 °C)–toluene (1:1)] (Found: C, 64.05; H, 5.4; N, 12.4. $C_{24}H_{24}N_4O_5$ requires C, 64.3; H, 3.4; N, 12.5%); (ii) 1-(2-*methoxy*-4-*methylphenyl*)-2-*phenylbutan*-1-*one* (**15**) (7.1 g, 22%) as crystals, m.p. 38.5—40 °C [from light petroleum (b.p. 60—80 °C)] (Found: C, 80.8; H, 7.8. $C_{18}H_{20}O_2$ requires C, 80.6; H, 7.5%); $\nu_{max.}$ 1 665 cm^{-1} (C=O str); δ($CDCl_3$; 60 MHz) 0.88 (3 H, t, *J* 6 Hz, $CHCH_2$*Me*), 1.50—2.50 (2 H, m, $CHCH_2$Me), 2.30 (3 H, s, ArMe), 3.80 (3 H, s, ArOMe), 4.52 (1 H, t, *J* 6 Hz, C*H*Et), 6.50—6.85 (2 H, m, ArH *ortho* to Me), 6.90—7.45 (5 H, m, Ph), and 7.30—7.65 (1 H, m, ArH *meta* to Me); *m/z* 268 ($M^{+\bullet}$, 0.5%) and 149 (M^+ − PhCHEt, 100).

Addition of identical amounts of tris(dipivalomethanato)-europium(III) to solutions of compounds (**14**) and (**15**) in deuteriochloroform gave the following shifts to higher frequency in p.p.m. compound (**14**): Ar*Me* = 0.60, ArO*Me* = 0.12; compound (**15**): Ar*Me* = 0.10, ArO*Me* = 0.45.

A mixture of the methyl ether (**14**) (10 g, 37 mmol) and pyridine hydrochloride (10.8 g, 94 mmol) was heated under reflux (*ca.* 200 °C) for 2.5 h. The mixture was then cooled and partitioned between dilute hydrochloric acid (1.5M; 150 ml) and ether (150 ml, then 2 × 100 ml). The combined ether layers were washed with saturated brine (100 ml), dried with sodium sulphate, and concentrated. Chromatography of the residue [light petroleum (b.p. 60—80 °C) then dichloromethane] gave 1-(4-*hydroxy*-2-*methylphenyl*)-2-*phenylbutan*-1-*one* (**7**) (7.3 g, 77%), m.p. 80—82 °C (from light petroleum) (Found: C, 80.1; H, 7.3. $C_{17}H_{18}O_2$ requires C, 80.3; H, 7.1%); $\nu_{max.}$ 1 660 cm^{-1} (C=O str) and 3 100—3 700 cm^{-1} (O–H str); *m/z* 254 ($M^{+\bullet}$, 6%) and (M^+ − PhCHEt, 100).

rel-(1R,2S)-1-{4-[2-(*Dimethylamino*)*ethoxy*]*phenyl*}-1-(4-*hydroxy*-2-*methylphenyl*)-2-*phenylbutan*-1-*ol* (**12**).—A solution of n-butyl-lithium in hexane (1.6M; 6.15 ml, 9.8 mmol) was added dropwise during 10 min to a stirred solution of 1-bromo-4-[2-(dimethylamino)ethoxy]benzene[8] (**5**) (2.4 g, 9.8 mmol) in dry THF (5 ml) at −78 °C under nitrogen. After 30 min, a solution of the ketone (**7**) (1.0 g, 3.9 mmol) in dry THF (5 ml) was added and the mixture allowed to reach room temperature. After 20 h, the mixture was partitioned between water (50 ml) and ether (100 ml, then 3 × 30 ml). The combined ether layers were washed with saturated brine (5 ml), dried with sodium sulphate, and concentrated. The residue was crystallised from toluene to give the tertiary alcohol (**12**) as a solvate with toluene (1:1)—see crystal structure (1.54 g, 77%), m.p. 160.5—162 °C (Found: C, 79.4; H, 8.0; N, 3.0. $C_{27}H_{33}NO_3 \cdot C_7H_8$ requires C, 79.81; H, 7.93; N, 3.33%. Calc. for $C_{27}H_{33}NO_3 \cdot 0.8C_7H_8$: C, 79.38; H, 8.05; N, 2.84%).

Dehydration of the Tertiary Alcohol (**12**).—A solution of compound (**12**) (0.5 g) in ethanol (5 ml) and concentrated hydrochloric acid (2 ml) was stirred at 22 °C for 1 h, then adjusted to pH 11 with aqueous sodium hydroxide. The mixture was diluted with water (30 ml) and extracted with ether (4 × 30 ml). The combined ether layers were washed with saturated brine (10 ml), dried, and concentrated. Examination of the ^{1}H n.m.r. spectrum of the residue showed that it contained an 8:1 mixture of *E*-(**2a**) and *Z*-(**2b**) isomers. Crystallisation of this residue from methanol gave (*E*)-*trans*-4-hydroxy-2-methyltamoxifen (**2a**) (0.43 g, 45%), m.p. 180—181.5 °C, t.l.c. characteristics and ^{1}H n.m.r. spectrum identical with those of a sample prepared by method 1.

4-*Hydroxy*-2,3,5-*trimethyltamoxifen* (**3a**). [1-(4-*Hydroxy*-2,3,5-*trimethylphenyl*)-2-*phenylbutan*-1-*one*] (**8**).—A mixture of 2-phenylbutanoic acid (**9**) (15 g, 91 mmol), 2,3,6-trimethylphenol (18.7 g, 138 mmol), and trifluoroacetic anhydride (14.2 ml, 100 mmol) was stirred at 15—20 °C for 20 h, then poured into saturated sodium hydrogencarbonate solution (150 ml). When no more gas was evolved, the product was extracted with ether (3 × 200 ml), the combined organic layers washed with saturated brine (100 ml), dried with sodium sulphate, and concentrated. Chromatography of the residue [light petroleum (b.p. 60—80 °C)–dichloromethane (10:1)] gave 2,3,6-*trimethylphenyl*-2-*phenylbutanoate* (**16**) (16.2 g, 63%) as an oil, b.p. 146 °C at 1.2 mmHg (Found: C, 80.8; H, 7.85. $C_{19}H_{22}O_2$ requires C, 80.8; H, 7.85%); $\nu_{max.}$ 1 750 cm^{-1} (C=O str); δ[$(CD_3)_2SO$; 250 MHz] 0.94 (3 H, t, *J* 7.3 Hz, $CHCH_2$*Me*,

Table 3. Positional parameters and their estimated standard deviations in the crystal structure of the 1:1 complex of compound (**12**) and toluene[a]

Atom	*x*	*y*	*z*
O(1)	−0.255 9(2)	−0.226 6(2)	−0.178 1(2)
O(2)	0.246 3(2)	0.047 8(2)	0.291 0(2)
O(3)	−0.136 8(2)	−0.138 1(2)	0.308 1(2)
N(1)	0.402 1(3)	0.170 0(3)	0.338 4(3)
CMe	−0.060 2(4)	−0.247 6(4)	0.174 9(4)
C(1)	−0.171 9(3)	−0.120 1(3)	0.119 1(3)
C(2)	−0.133 9(3)	−0.197 3(3)	0.096 7(4)
C(3)	−0.164 9(3)	−0.230 4(3)	−0.003 5(4)
C(4)	−0.230 6(3)	−0.190 3(3)	−0.082 1(3)
C(5)	−0.266 3(3)	−0.113 5(3)	−0.063 3(4)
C(6)	−0.235 1(3)	−0.081 4(3)	0.036 5(4)
C(7)	−0.138 5(3)	−0.078 9(3)	0.226 1(3)
C(8)	−0.204 4(4)	−0.003 6(3)	0.241 6(4)
C(9)	−0.160 5(4)	0.041 4(3)	0.346 2(4)
C(10)	−0.218 9(5)	0.116 4(4)	0.363 4(5)
C(11)	−0.309 3(4)	−0.026 5(3)	0.232 8(4)
C(12)	−0.334 4(4)	−0.077 6(4)	0.307 8(4)
C(13)	−0.431 9(4)	−0.096 3(4)	0.300 4(5)
C(14)	−0.504 0(4)	−0.064 9(4)	0.222 4(5)
C(15)	−0.480 7(4)	−0.013 2(4)	0.149 0(5)
C(16)	−0.384 2(4)	0.006 1(4)	0.156 1(4)
C(17)	−0.034 5(3)	−0.047 8(3)	0.244 5(3)
C(18)	0.034 0(4)	−0.061 7(4)	0.336 5(4)
C(19)	0.127 9(4)	−0.031 2(4)	0.356 3(4)
C(20)	0.154 5(3)	0.016 5(3)	0.279 4(4)
C(21)	0.087 6(4)	0.030 7(4)	0.187 1(4)
C(22)	−0.004 8(4)	−0.000 5(3)	0.169 3(4)
C(23)	0.306 5(4)	0.056 9(4)	0.392 0(4)
C(24)	0.404 9(4)	0.087 6(4)	0.384 1(4)
C(25)	0.391 1(4)	0.236 4(4)	0.410 1(4)
C(26)	0.492 5(4)	0.185 5(4)	0.308 2(5)
C(31)	0.737 5(4)	0.224 7(4)	0.067 2(5)
C(32)	0.705 6(5)	0.175 7(4)	−0.019 9(5)
C(33)	0.773 4(5)	0.142 9(5)	−0.067 8(5)
C(34)	0.870 6(5)	0.157 2(4)	−0.030 6(5)
C(35)	0.901 8(5)	0.204 3(4)	0.056 3(6)
C(36)	0.834 8(5)	0.237 6(4)	0.106 2(5)
C(37)	0.666 5(6)	0.263 3(6)	0.120 7(6)

[a] C(31)–C(37) are of the toluene molecule.

1.30—2.20 (8 H, m, $CHCH_2Me$ and 2 × Me *ortho* to OCOR), 2.15 (3 H, s, Me *meta* to OCOR), 3.91 (1 H, t, *J* 7.7 Hz, $CHCH_2Me$), 6.90—6.94 (2 H, br s, ArH), and 7.26—7.48 (5 H, m, Ph); *m/z* 282 ($M^{+\bullet}$, 4%) and 91 ($PhCH_2^+$, 100). Further elution of the column [dichloromethane–light petroleum (b.p. 60—80 °C) (65:35)] gave the *title phenol* (**8**) (2.31 g, 9%), m.p. 78.5—80 °C [from light petroleum (b.p. 60—80 °C)–dichloromethane (1:1)] (Found: C, 81.2; H, 7.9. $C_{19}H_{22}O_2$ requires C, 80.8; H, 7.85%); $\nu_{max.}$ 1 650 (C=O str) and 3 100—3 700 cm^{-1} (O–H str); *m/z* 163 (M^+ − PhCHEt, 100%), molecular ion not observed.

rel-(1R,2S)-1-{4-[2-(*Dimethylamino*)*ethoxy*]*phenyl*}-1-(4-*hydroxy*-2,3,5-*trimethylphenyl*)-2-*phenylbutan*-1-*ol* (**13**).—The procedure for the preparation of (**12**) was followed but using the ketone (**7**) (1 g, 3.55 mmol). The crude product was crystallised from toluene to give the *title compound* (**13**) (1.07 g, 68%), m.p. 177—178 °C (Found: C, 78.0; H, 8.3; N, 2.9. $C_{29}H_{37}NO_3$ requires C, 77.8; H, 8.3; N, 3.1%).

Dehydration of the Tertiary Alcohol (**13**).—The tertiary alcohol (**13**) (4.0 g) was dehydrated using the same method as for the dehydration of (**12**). The crude product mixture was crystallised from light petroleum (b.p. 80—100 °C)–toluene (1:1) to give trans-1-{4-[2-(*dimethylamino*)*ethoxy*]*phenyl*}-1-(4-*hydroxy*-2,3,5-*trimethylphenyl*)-2-*phenyl*-(E)-*but*-1-*ene* (4-*hydroxy*-2,3,5-*trimethyltamoxifen*) (**3a**) (3.11 g, 81%), m.p. 97—101 °C (Found: C, 81.5; H, 8.3; N, 2.95. $C_{29}H_{35}NO_2$ requires C, 81.1; H, 8.2; N, 3.3%). The mother liquor from the crystallisation of the *E* isomer was concentrated and the residue crystallised from ether to give the *Z-cis-isomer* (**3b**) (0.14 g, (3.5%), m.p. 133—135 °C (Found: C, 81.2; H, 8.3; N, 3.1. $C_{29}H_{35}NO_2$ requires C, 81.1; H, 8.2; N, 3.3%).

1-(4-*Methoxyphenyl*)-1-(4-*methoxy*-2-*methylphenyl*)-2-*phenyl*-(E)-*but*-1-*ene* (**19**).—The title compound was prepared from 4-bromo-3-methylanisole[22] (2.4 g, 11.9 mmol) and 1-(4-methoxyphenyl)-2-phenylbutan-1-one[12] (2.54 g, 10 mmol) essentially by the method described for the preparation and dehydration of the tertiary alcohol (**12**). It was isolated by column chromatography [10% dichloromethane in light petroleum (b.p. 40—60 °C)] as an 8:1 mixture of *E* and *Z* isomers (as determined from the ratio of signals for methoxy groups in the ^1H n.m.r. spectrum) (2.92 g, 86%), m.p. 64—66 °C (Found: C, 83.55; H, 7.5. $C_{25}H_{26}O_2$ requires C, 83.8; H, 7.31%).

Isomerisation Studies.—4-Hydroxy-2-methyltamoxifen (**2a**) and 4-hydroxy-2,3,5-trimethyltamoxifen (**3a**) were allowed to isomerise as described in the text. In one experiment, (**2a**) (3.5 mg) and (**3a**) (3.5 mg) were dissolved in deuteriochloroform (0.5 ml) in a 5 mm n.m.r. tube which was maintained at 47 °C in the spectrometer while spectra were run at intervals. The relative proportions of (**2a**), (**3a**), (**2b**), and (**3b**) were monitored by measuring the intensities of the triplets for the $MeCH_2$ proton signals centred at 0.815, 0.995, 0.80, and 0.98 respectively. The following ratios for (**2a**)/(**2b**) and (**3a**)/(**3b**) were recorded: 2 h: 16 and 8; 4 h: 11.5 and 5; 18 h: 4.5 and 3.2. The solution was then maintained at 60 °C. After 10 h the ratios were 3.1 and 3.0. In a separate experiment, solutions of (i) (**2a**) (3.5 mg) + (**3a**) (3.5 mg) and (ii) (**2a**) (7.0 mg) were prepared in deuteriochloroform (0.5 ml). These solutions were maintained at 60 °C for 1 h before examination by n.m.r. spectroscopy. Ratios found were for sample (i): (**2a**)/(**2b**) = 21.7 and (**3a**)/(**3b**) = 10.9, and for sample (ii): (**2a**)/(**2b**) = 12.1.

X-*Ray Crystal Structure Determination of Compound* (**12**).—*Crystal data:* $C_{34}H_{41}NO_3$ ($C_{27}H_{33}NO_3$ + toluene 1:1), *M* = 511.71. Monoclinic, *a* = 14.267(4), *b* = 16.059(7), *c* = 13.264(3) Å, β = 104.84(1)°, *U* = 2 937(3) Å^3, D_m = 1.16 g cm^{-3}, *Z* = 4, D_x = 1.157 g cm^{-3}, *F*(000) = 1 104, space group $P2_1/c$, Cu-K_α radiation, μ = 5.36 cm^{-1}. Transparent plate-like crystals were grown from toluene solution. *X*-Ray photographs were taken to determine cell parameters and crystal class.

Data Collection and Processing.—Accurate cell dimensions were obtained by least-squares analysis of 25 θ values measured on an Enraf-Nonius CAD-4 diffractometer. Intensity data were collected on the diffractometer with Ni-filtered Cu-K_α radiation, operated in the ω/2θ scan mode up to θ = 50°. The crystal employed for the diffraction study had the dimensions 0.21 × 0.25 × 0.08 mm. The intensity of three standard reflections were monitored at intervals of 3 600 s and no crystal decomposition was observed. Out of 3 009 unique reflections, 1937 with $I > 1.5\sigma(I)$ were used for the refinement.

Structure Analysis and Refinement.—The structure was solved by the direct methods with the use of MULTAN 82[23] and refined on *F* by full-matrix least-squares procedures with anisotropic thermal parameters for non-hydrogen atoms. All the hydrogen atoms were located from difference Fourier

Table 4. Bond lengths (Å) and bond angles (°) with their estimated standard deviations for compound (**12**)

Bond lengths			
O(1)–C(4)	1.363(5)	C(7)–C(17)	1.525(6)
O(2)–C(20)	1.374(5)	C(8)–C(9)	1.548(8)
O(2)–C(23)	1.401(6)	C(8)–C(11)	1.516(7)
O(3)–C(7)	1.440(5)	C(9)–C(10)	1.515(7)
N(1)–C(24)	1.452(6)	C(11)–C(12)	1.405(9)
N(1)–C(25)	1.463(8)	C(11)–C(16)	1.377(7)
N(1)–C(26)	1.465(7)	C(12)–C(13)	1.402(8)
CMe–C(2)	1.508(7)	C(13)–C(14)	1.356(9)
C(1)–C(2)	1.415(7)	C(14)–C(15)	1.383(10)
C(1)–C(6)	1.376(6)	C(15)–C(16)	1.390(6)
C(1)–C(7)	1.527(6)	C(17)–C(18)	1.372(6)
C(2)–C(3)	1.394(6)	C(17)–C(22)	1.404(7)
C(3)–C(4)	1.371(6)	C(18)–C(19)	1.388(6)
C(4)–C(5)	1.382(7)	C(19)–C(20)	1.403(6)
C(5)–C(6)	1.384(6)	C(20)–C(21)	1.364(6)
C(7)–C(8)	1.578(7)	C(21)–C(22)	1.373(6)
		C(23)–C(24)	1.515(7)
Bond angles			
C(20)–O(2)–C(23)	118.7(3)	C(7)–C(8)–C(11)	114.4(4)
C(24)–N(1)–C(25)	112.8(4)	C(9)–C(8)–C(11)	110.3(5)
C(24)–N(1)–C(26)	109.7(4)	C(8)–C(9)–C(10)	113.2(5)
C(25)–N(1)–C(26)	107.6(4)	C(8)–C(11)–C(12)	120.8(5)
C(2)–C(1)–C(6)	115.9(4)	C(8)–C(11)–C(16)	121.9(4)
C(2)–C(1)–C(7)	122.0(4)	C(12)–C(11)–C(16)	117.1(5)
C(6)–C(1)–C(7)	121.9(4)	C(11)–C(12)–C(13)	120.2(6)
CMe–C(2)–C(1)	124.2(4)	C(12)–C(13)–C(14)	121.4(6)
CMe–C(2)–C(3)	116.5(4)	C(13)–C(14)–C(15)	119.1(5)
C(1)–C(2)–C(3)	119.3(4)	C(14)–C(15)–C(16)	120.0(5)
C(2)–C(3)–C(4)	122.2(4)	C(11)–C(16)–C(15)	122.2(4)
O(1)–C(4)–C(3)	118.4(4)	C(7)–C(17)–C(18)	122.1(4)
O(1)–C(4)–C(5)	122.0(4)	C(7)–C(17)–C(22)	121.5(4)
C(3)–C(4)–C(5)	119.6(4)	C(18)–C(17)–C(22)	116.4(4)
C(4)–C(5)–C(6)	117.5(4)	C(17)–C(18)–C(19)	122.9(4)
C(1)–C(6)–C(5)	125.3(4)	C(18)–C(19)–C(20)	118.9(4)
O(3)–C(7)–C(1)	110.9(4)	O(2)–C(20)–C(19)	123.0(4)
O(3)–C(7)–C(8)	107.6(4)	O(2)–C(20)–C(21)	117.8(4)
O(3)–C(7)–C(17)	105.5(3)	C(19)–C(20)–C(21)	119.1(4)
C(1)–C(7)–C(8)	113.5(4)	C(20)–C(21)–C(22)	120.9(4)
C(1)–C(7)–C(17)	110.5(4)	C(17)–C(22)–C(21)	121.8(4)
C(8)–C(7)–C(17)	108.4(4)	O(2)–C(23)–C(24)	108.7(4)
C(7)–C(8)–C(9)	110.9(4)	N(1)–C(24)–C(23)	113.5(5)

synthesis and their positional and isotropic thermal factors were refined except for those of H(MEA), H(25c), H(26c), H(37a), H(37b), and H(37c). The final difference Fourier map did not show any peaks >0.18 e Å^{-1}. The final R value was 0.052. A unit weight was assigned to each reflection. The maximum shift/error was 0.07 for non-hydrogen atoms and 0.13 for hydrogen atoms. Empirical absorption[24] and extinction corrections were applied. Atomic scattering factors were taken from reference 25. All calculations were performed on PDP 11/34A and VAX 750 computers using the SDP program system.[26] Tables 3 and 4 give positional parameters and bond lengths and angles.*

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* *Supplementary data* (see section 5.6.3 of Instructions for authors, in the January issue). Fractional atomic co-ordinates, hydrogen-atom co-ordinates, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre.

References

1 C. P. Daniel, S. J. Gaskell, H. Bishop, and R. I. Nicholson, *J. Endocrinol.*, 1979, **83**, 401.
2 V. C. Jordan, M. M. Collins, L. Rowsby, and G. Prestwich, *J. Endocrinol.*, 1977, **75**, 305.
3 R. I. Nicholson, J. S. Syne, C. P. Daniel, and K. Griffiths, *Eur. J. Cancer*, 1979, **15**, 317.
4 A. B. Foster, M. Jarman, O.-T. Leung, R. McCague, G. Leclercq, and N. Devleeschouwer, *J. Med. Chem.*, 1985, **28**, 1491.
5 M. J. K. Harper and A. L. Walpole, *Nature (London)*, 1966, **212**, 87.
6 V. C. Jordon, B. Haldemann, and K. E. Allen, *Endocrinology*, 1981, **108**, 1353.
7 D. W. Robertson and J. A. Katzenellenbogen, *J. Org. Chem.*, 1982, **47**, 2387.
8 P. C. Ruenitz, J. R. Bagley, and C. M. Mokler, *J. Med. Chem.*, 1982, **25**, 1056.
9 B. S. Katzenellenbogen, M. J. Norman, R. L. Eckert, S. W. Peltz, and W. F. Mangel, *Cancer Res.*, 1984, **44**, 112.
10 J. A. Katzenellenbogen, K. E. Carlson, and B. S. Katzenellenbogen, *J. Steroid Biochem.*, 1985, **22**, 589.
11 R. Kuroda, S. Cutbush, S. Neidle, and O.-T. Leung, *J. Med. Chem.*, 1985, **28**, 1497.
12 M. Jarman and R. McCague, *J. Chem. Res.*, 1985, (*S*), 116; (*M*), 1342.
13 D. J. Cram and K. R. Kopecky, *J. Am. Chem. Soc.*, 1959, **81**, 2748.
14 P. Sohar, G. Schneider, G. Abraham, T. Horvath, and Z. Mehesfalvi, *Acta Chim. Acad. Sci. Hung.*, 1980, **105**, 201.
15 R. McCague, *J. Chem. Soc., Perkin Trans. 1*, 1987, 1011.
16 G. R. Bedford and D. N. Richardson, *Nature (London)*, 1966, **212**, 733.
17 P. Sohar, G. Abraham, G. Schneider, T. Horvath, and E. Fuggerth, *Acta Chim. Acad. Sci. Hung.*, 1979, **100**, 69.
18 R. McCague, *J. Chem. Res. (M)*, 1986, 771.
19 D. J. Collins, J. J. Hobbs, and C. W. Emmens, *J. Med. Chem.*, 1971, **14**, 952.
20 S. D. Cutbush, S. Neidle, A. B. Foster, and F. Leclercq, *Acta Crystallogr., Sect. B*, 1982, **38**, 1024.
21 G. Precigoux, C. Courseille, S. Geoffre, and M. Hospital, *Acta Crystallogr., Sect. B*, 1979, **35**, 3070.
22 O. A. Zeide and B. M. Dubinin, *J. Gen. Chem. USSR (Engl. Transl.)*, 1932, **2**, 455 (*Chem. Abstr.*, 1933, **27**, 963).
23 P. Main, S. J. Fiske, S. E. Hull, L. Lessinger, G. Germain, J.-P. Leclercq, and M. M. Woolfson, 'MULTAN 82. A System of Computer Programs for the Automatic Solution of Crystal Structures from *X*-Ray Diffraction Data,' University of York, York, 1982.
24 N. Walker and D. Stuart, *Acta Crystallogr., Sect. A*, 1983, **34**, 158.
25 D. T. Cromer and J. T. Waber in 'International Tables for *X*-Ray Crystallography,' Kynoch Press, Birmingham, 1974, vol. VI, p. 99.
26 B. A. Frenz, 'Enraf-Nonius Structure Determination Package,' Enraf-Nonius, Delft, 1980.

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