containing the same culture medium and cultured at 37 °C in humidified air–CO_2 (95:5). After 24 h, a solution of tamoxifen or a derivative in ethanol was added (0.1% final concentration of ethanol), and after 48 h, the medium was replaced by fresh medium containing tamoxifen or a derivative for an additional 72 h. Both at 24 h (drug addition) and at 144 h (end of experiment) the cells were washed twice with Earle's base (2 mL) and suspended in trypsin–EDTA (1.5 mL). The DNA of the collected cells was precipitated with 0.5 M perchloric acid and quantified by the diphenylamine method.[34] Quadruplicate cultures were used throughout.

Acknowledgment. This investigation was supported by a program grant to the Drug Metabolism Team, Drug Development Section, Institute of Cancer Research, by the Cancer Research Campaign and the Medical Research Council and by grants to the Institut Jules Bordet from the Fonds Cancérologique de la Caisse Générale d'Epargne et Retrait de Belgique. We thank Dr. H. K. Adam (I.C.I. Pharmaceuticals) for a sample of 4-hydroxytamoxifen and M. H. Baker for technical assistance.

(34) Burton, K. *Biochem. J.* **1976**, *62*, 315.

Registry No. **5**, 65213-48-1; **6**, 82413-20-5; **9**, 57999-46-9; **10**, 68047-07-4; **11**, 97150-94-2; **12**, 68047-06-3; **13**, 83647-29-4; **14**, 97150-95-3; **15**, 97150-96-4; **15**·HCl, 97150-97-5; **17**, 97150-98-6; **18**, 78423-10-6; **19**, 97135-10-9; **20**, 97150-99-7; **21**, 96474-35-0; *trans*-(*E*)-**22**, 97151-00-3; *cis*-(*Z*)-**22**, 61923-53-3; *trans*-(*E*)-**23**, 19118-19-5; *cis*-(*Z*)-**23**, 97151-01-4; *trans*-(*E*)-**24**, 97151-02-5; *cis*-(*Z*)-**24**, 97170-41-7; *trans*-(*Z*)-**25**, 97151-03-6; *cis*-(*E*)-**25**, 97151-04-7; *trans*-(*Z*)-**26**, 97151-05-8; *cis*-(*E*)-**26**, 97151-06-9; Cl-$(CH_2)_2NMe_2$, 4584-46-7; CH_3CHO, 75-07-0; 4-(tetrahydropyran-2-yloxy)phenyl bromide, 36603-49-3; 1-[4-[2-(dimethylamino)-ethoxy]phenyl]-2-phenyl-1-[4-(tetrahydropyran-2-yloxy)-phenyl]-1-butanol, 68047-08-5; 3-(tetrahydropyran-2-yloxy)phenyl bromide, 57999-49-2; *o*-tolyl bromide, 95-46-5; 1-[4-[2-(dimethylamino)ethoxy]phenyl]-1-(2-methylphenyl)-2-phenyl-1-butanol, 97151-07-0; 2,4-bis(tetrahydropyran-2-yloxy)phenyl bromide, 31963-61-8; 1-[2,4-bis(tetrahydropyran-2-yloxy)-phenyl]-1-[4-[2-(dimethylamino)ethoxy]phenyl]-2-phenyl-1-butanol, 97170-42-8; 2-methyl-4-(tetrahydropyran-2-yloxy)phenyl bromide, 97151-08-1; 1-[4-[2-(dimethylamino)ethoxy]phenyl]-1-[4-(tetrahydropyran-2-yloxy)-2-methylphenyl]-2-phenyl-1-butanol, 97151-09-2; (*E*)-1-[4-[2-(dimethylamino)ethoxy]phenyl]-1,2-diphenylethene, 97151-10-5; (*Z*)-1-[4-[2-(dimethylamino)ethoxy]phenyl]-1,2-diphenylethene, 97151-11-6; oxetane, 503-30-0; ethylene oxide, 75-21-8.

Structural Studies on Some Tamoxifen Derivatives

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The crystal structures of four derivatives of the antiestrogenic drug tamoxifen are described. These are of 2-hydroxy-, 3-hydroxy-, and 2-methyl-4-hydroxytamoxifen and of 1-(4-methoxyphenyl)-2-phenyl-1-[(tetrahydropyran-2-yloxy)phenyl]-1-butanol, the synthetic precursor to 2-hydroxytamoxifen. All compounds have trans stereochemistry about the ethylene double bond, as in tamoxifen itself. The orientations of the hydroxy substituents have been found to differ by 180°, depending on the nature of the compound. Empirical energy calculations have been used to show that the barrier to free rotation for the hydroxy-substituted phenyl rings is too high for interconversion to take place. These orientational differences are, it is suggested, related to the marked differences in estrogen receptor binding ability.

The accompanying paper reports synthesis, receptor-binding, and biological data for *trans*-tamoxifen derivatives with hydroxy and methyl substitution at several positions on the phenyl ring cis to the ethyl group on the ethene moiety. This study reports the molecular structures of several of these: 2- and 3-hydroxy- and 2-methyl-4-hydroxytamoxifen, as well as that of the synthetic precursor to the 2-hydroxy compound, 1-(4-methoxyphenyl)-1-[2-(tetrahydropyran-2-yloxy)phenyl]-2-phenyl-1-butanol. All have been determined by X-ray crystallography. The conformational dynamics of these molecules has been examined by semiempirical energy calculations in order to ascertain (i) whether the ground-state crystal structures correspond to unique energy minima and (ii) what the energy pathways between different conformers are. These studies have defined the stereochemistries of the derivatives and their relationships to both isomerization properties and estrogen receptor binding abilities.[1]

The molecular structures of a number of tamoxifen derivatives have now been determined. Both parents compounds *cis*-[2] and *trans*-tamoxifen[3] have been examined, as well as their 4-iodo derivatives,[4] and a synthetic precursor to *trans*-tamoxifen that contains only the methoxy part of the full side chain.[5] Both clomiphene[6] (with chlorine replacing the ethyl group) and the 1-(*p*-2-pyrrolidinineethoxyphenyl) derivative nafoxidine[7] have antiestrogenic activity and retain the trans arrangement.

These molecular structures have been examined in terms of their possible interrelationships[7] and also in relation to the structures of the estrogens estradiol and diethylstilbesterol.[8]

Experimental Section

Crystal Data. The 2-hydroxy and 2-methyl-4-hydroxy compounds were recrystallized from methanol; the 3-hydroxy com-

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(1) Foster, A. B.; Jarman, M.; Leung, O.-T.; McCague, R.; Leclercq, G.; Devleeschouwer, N. *J. Med. Chem.*, preceding paper in this issue.
(2) Kilbourn, B. T.; Owston, P. G. *J. Chem. Soc. B* **1970**, 1.
(3) Precigoux, G.; Coursielle, C.; Geoffre, S.; Hospital, M. *Acta Crystallogr., Sect. B: Struct. Crystallogr. Cryst. Chem.* **1979**, *35*, 3070.
(4) Hunter, D. H.; Payne, N. C.; Rahman, A.; Richardson, J. F.; Ponce, Y. Z. *Can. J. Chem.* **1983**, *61*, 421.
(5) Cutbush, S. D.; Neidle, S.; Foster, A. B.; Leclercq, F. *Acta Crystallogr., Sect. B: Struct. Crystallogr. Cryst. Chem.* **1982**, *38*, 1024.
(6) Ernst, S.; Hite, G. *Acta Crystallogr., Sect. B: Struct. Crystallogr. Cryst. Chem.* **1976**, *32*, 291.
(7) Camerman, N.; Chan, L. Y. Y.; Camerman, A. *J. Med. Chem.* **1980**, *23*, 941.
(8) Daux, W. L.; Griffin, J. F.; Rohrer, D. C.; Weeks, C. M. In "Hormone Antagonists"; Agarwal, M. K., Ed.; Walter de Gruyter and Co.: New York, 1982; p 3.

0022-2623/85/1828-1497$01.50/0

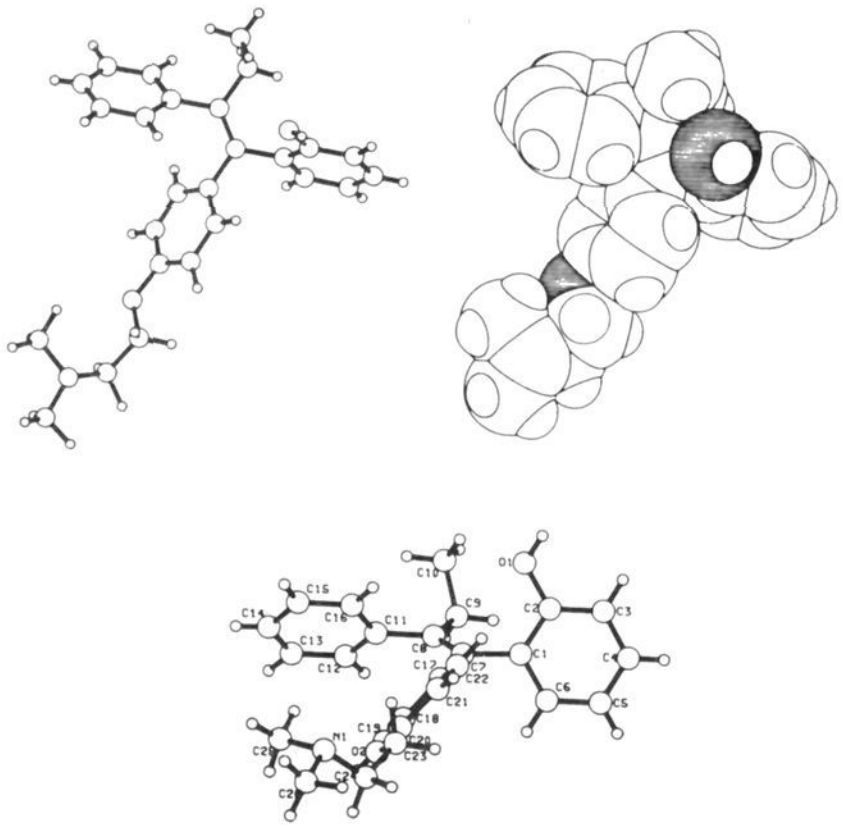


Figure 1. Computer-drawn representations of the molecular structure of 2-hydroxytamoxifen. Upper representations are projected in the plane of the C1–C7 bond, with that at the right having atoms drawn at their van der Waals radii and oxygen atoms being shaded. Lower representation shows the numbering scheme used and is projected in the plane of the 1-substituted phenyl ring.

pound was recrystallized from acetonitrile and the synthetic precursor from 60:80 petroleum ether. Preliminary X-ray data were obtained with Weissenberg and oscillation photography oscillation photography; subsequent accurate cell dimensions were obtained on an Enraf-Nonius CAD4 diffractometer, operated at 24 °C, by least-squares refinement of 25 θ values. Intensity measurements were made on the diffractometer with an ω–2θ scan technique and Ni-filtered Cu Kα radiation (λ = 1.541 78 Å). For each compound, the intensities of three standard reflections were periodically monitored; in no case was significant crystal decay found. Table I details crystal and other experimental data. Absorption corrections were not applied to the intensity data sets in view of the low value for the absorption coefficients.

The structures were solved without difficulty by application of the MULTAN-82 direct-methods computer program.[9] In each case, the correct positions of non-hydrogen atoms were located in the *E*-map corresponding to the phase set with the highest combined figure of merit. Subsequent refinements were performed by the full-matrix least-squares method, minimizing the function $w(|F_o| - |F_c|)^2$. Initially, unit weights were used. The positions of hydrogen atoms were found in difference Fourier electron density maps. Final refinements varied non-hydrogen atom positional and anisotropic thermal parameters and hydrogen atom positional and isotropic thermal parameters (except for the case of 3-hydroxy derivative, for which some hydrogen atom positions were calculated and all hydrogen atom parameters were kept fixed). A weighting scheme with $w = 1/\sigma^2(F_o) + 0.03F_o^2$ was found to produce acceptably invarient F_o/F_c agreement over ranges of F_o, θ, and hkl. Final reliability indices are given in Table I. Final non-hydrogen atoms fractional coordinates are given in Table II. Other coordinates and structure factor data are available from S.N.

All calculations were performed on a PDP11/34 computer using the SDP program. Atomic scattering factors were taken from ref 10.

(9) Main, P.; Fiske, S. J.; Hull, S. E.; Lessinger, L.; Germain, G.; Leclercq, J.-P.; Woolfson, M. M. "Multan-82, A System of Computer Programs for the Automatic Solution of Crystal Structures from X-ray Diffraction Data"; University of York: York, England, 1982.

(10) Cromer, D. T.; Waber, J. T. In "International Tables for X-ray Crystallography"; Kynoch Press: Birmingham, England, 1974; Vol. IV, p 99.

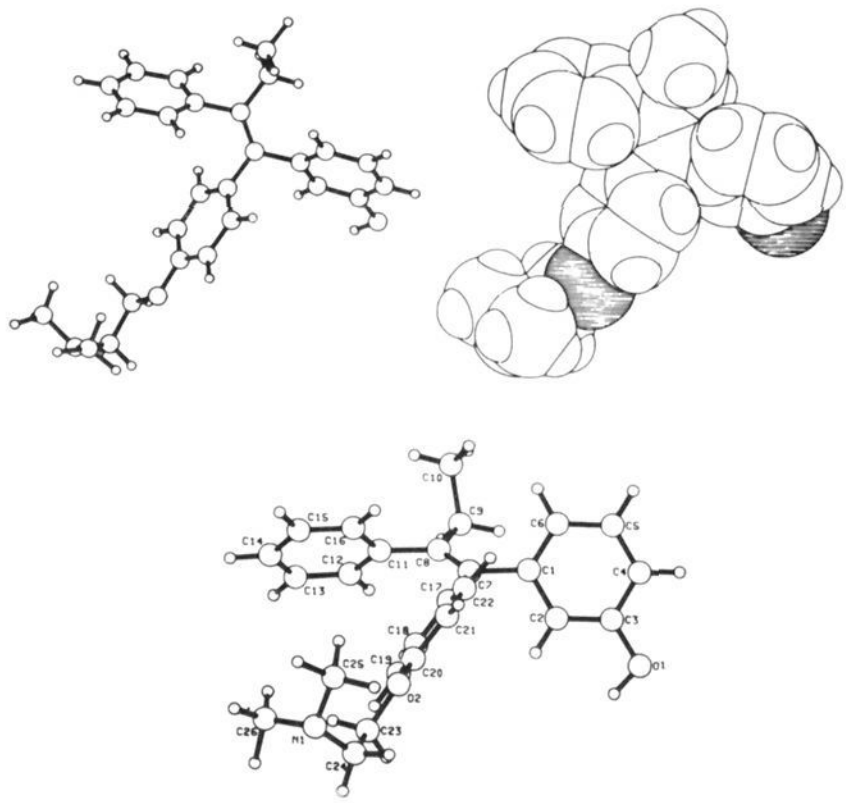
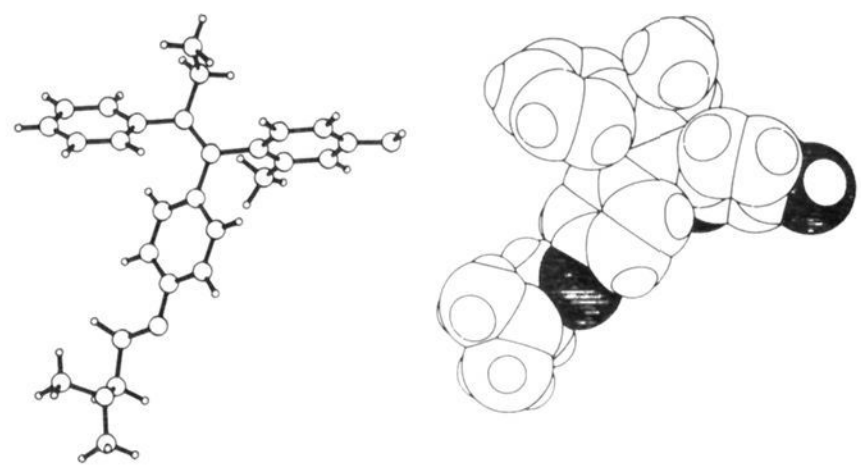


Figure 2. Molecular structure of 3-hydroxytamoxifen. Projections shown are as in Figure 1.



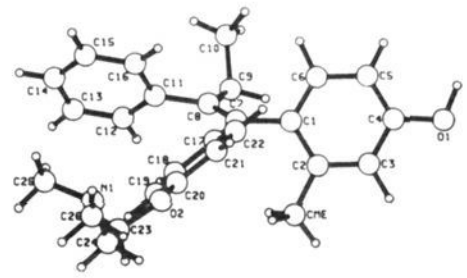


Figure 3. Molecular structure of 2-methyl-4-hydroxytamoxifen. Projections shown are as in Figure 1.

Energy and Computer Graphics Calculations. The intramolecular energy of a particular conformation was approximated to be

$$E_{TOT} = E_{NB} + E_{TORS}$$

where the nonbonded energy is defined as

$$E_{NB} = A/r^6 - B/r^{12}$$

and parameters A and B were chosen so that atoms could approach closer together (by up to ca. 0.2 Å) than the sum of their van der Waals radii. In this way, it was possible to at least in part compensate for the absence of explicit bond angle and bond length deformation terms in the above summation.

The torsion potential was defined as

$$E_{TORS} = E_o[1 + \cos(n\psi)]$$

and barrier heights (E_o) of 0.3 and 1.2 kcal mol^{-1} were used for

(11) Hopfinger, A. J. "Conformational Properties of Macromolecules"; Academic Press: New York, 1973; p 21.

Table I. Crystallographic Data

	2-OH-T	3-OH-T	2-Me-4-OH-T	2-OH-precursor-T
mol formula	$C_{26}H_{29}O_2N$	$C_{26}H_{29}O_2N$	$C_{27}H_{31}O_2N$	$C_{28}H_{32}O_4$
M_r	387.53	387.53	401.55	432.56
a, Å	9.942 (1)	14.487 (2)	22.586 (2)	9.970 (1)
b, Å	10.583 (2)	5.976 (1)	15.402 (3)	10.657 (1)
c, Å	11.088 (1)	25.609 (3)	13.767 (2)	12.400 (1)
α, deg	84.59 (1)			94.76 (1)
β, deg	76.82 (1)	100.28 (1)	103.46 (1)	78.22 (1)
γ, deg	75.72 (2)			109.14 (1)
V, Å^3	1099.8	2181.5 (1.0)	4657.5	1218.3 (5)
Z	2	4	8	2
calcd density, g cm^{-3}	1.17	1.180	1.145	1.179
space gp	$P\bar{1}$	$P2_1/c$	$C2/c$	$P\bar{1}$
μ, cm^{-1}	5.38	5.43	5.23	5.83
no. of unique reflcns	3050	3250	3448	4591
no. of reflcns used in refinement	2017 with $I \geq 2\sigma(I)$	2348 with $I \geq 1.5\sigma(I)$	2585 with $I \geq 2\sigma(I)$	3826 with $I \geq 1.5\sigma(I)$
θ_{max}, deg	60	60	60	70
R	0.0430	0.0485	0.0442	0.0511
R_w	0.0510	0.0464	0.0544	0.0471
max parameter shift in final cycle	0.34	0.03	0.13	0.10
highest peak in ΔF map, e/Å^3	0.23	0.24	0.19	0.15

C–phenyl and C(sp^3)–C(sp^3) bonds, respectively. Electrostatic contributions to the total energy were not taken into account as it was considered that they would not be major factors in the differentiation of distinct conformers, which was the major objective of the energy calculations in this study.

These calculations and concomitant interactive computer graphics studies were performed on a PDP11/34 computer linked to a Supervisor 214 graphics system (Gresham-Lion Ltd.).

Results and Discussion

Molecular Structures. Figures 1–4 show computer-drawn projections of the molecular structures determined by the crystallographic analyses. All four compounds have the ethyl group and the 4-substituted phenyl ring attached to the central ethylene moiety, in a trans orientation with respect to each other. The compounds are therefore confirmed to have the same configuration as tamoxifen itself.

It is characteristic of both *cis*- and *trans*-tamoxifens and their derivatives that they adopt a propeller conformation with respect to the triphenylethylene system. The four substituted tamoxifens reported here all have this feature (Table III), with the interplane dihedral angles being very comparable. Steric hindrance at the 2-positions in the 2-methyl-4-hydroxy and 2-hydroxy precursor structures has had little effect on the dihedral angles of the propeller; differences between structures are probably attributable to crystal forces. Energy calculations (see below) on the barriers to rotation about the C–phenyl single bonds indicate that the energy minima are relatively broad though well-defined. The noncoplanarity of the phenyl rings with the ethylene bond is the consequence of nonbonded interactions between the rings and with the ethyl group. This has the effect of distorting the bond angles around atoms C7 and C8 from their ideal 120° sp^2 values (Table IV), so that the angles C1–C7–C17 and C9–C8–C11 are compressed by 5–7° in all the three triphenylethene structures reported here. Most bond lengths do not deviate significantly from standard values. For example, the exocyclic C–phenyl bonds (C1–C7, C7–C17, C8–C11) are equivalent within experimental error. Their mean values are 1.494 Å for the three triphenylethene structures and 1.533 Å for the triphenylethene precursor structure.

The conformation of the (dimethylamino)ethoxy side chain shows a high degree of flexibility. The N–C–C–O torsion angle is –76.7° (gauche$^-$) in tamoxifen itself; this conformation is shown by the 2-hydroxy derivative whereas the 3-hydroxy and 2-methyl-4-hydroxy derivatives both have gauche$^+$ arrangements (Table V) and nafoxidine (with the nitrogen atom protonated) has a trans one. *cis*-Tamoxifen has two independent molecules in the asymmetric unit, one of which has a gauche$^+$ N–C–C–O side chain torsion angle while the other has a trans value. Thus, the position of the nitrogen atom relative to the rest of the molecule is very flexible. However, it is not possible to state whether or not receptor binding requires a rigid or flexible side chain.

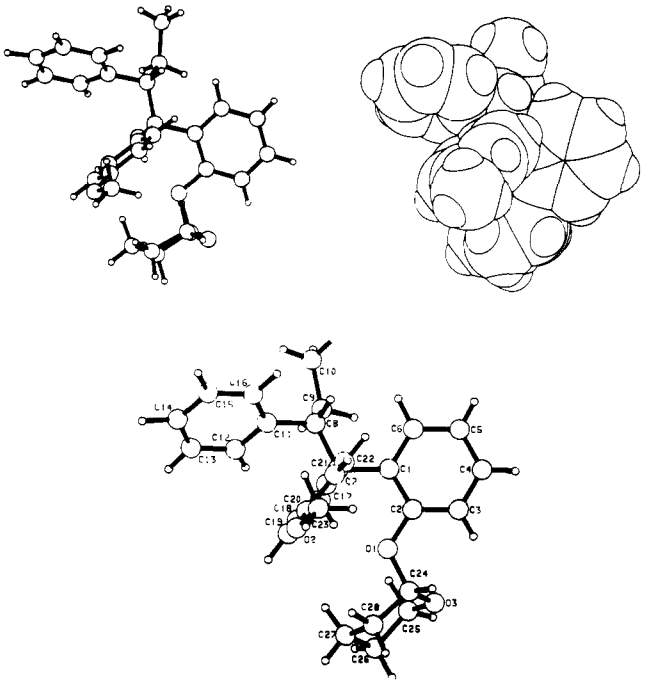


Figure 4. Molecular structure of the synthetic precursor to 2-hydroxytamoxifen (see text). Projections shown are as in Figure 1.

The introduction of hydroxy or methyl substitution in the phenyl ring cis to the ethyl group has introduced a new structural feature into the tamoxifen series. Figures 1 and 2 show that the hydroxyl groups at positions 2 and 3 (in the 2- and 3-hydroxy derivatives, respectively) are oriented quite differently, when the molecular structures are displayed from identical viewpoints. Thus, the 2-hydroxy compound has the 2-hydroxy group projecting out from the "front" face of the molecule, as shown. The 3-hydroxy compound, on the other hand, is oriented on the "back" face. The 2-methyl-4-hydroxy compound (Figure 3) likewise has its 2-methyl group oriented on the rear molecular face. These differences are quantitated by the torsion

Table II. Atomic Positional and Thermal Parameters with Estimated Standard Deviations in Parentheses

atom	x	y	z	B_{eq}, Å^2	atom	x	y	z	B_{eq}, Å^2
				2-OH-T					
O1	−0.4626 (2)	−0.2858 (2)	0.3693 (2)	5.80 (6)	H1	−0.552 (4)	−0.240 (4)	0.412 (4)	12 (1)
O2	−0.2219 (3)	−0.1046 (2)	−0.3209 (2)	5.54 (6)	H3	−0.636 (3)	−0.439 (3)	0.418 (3)	6.0 (8)
N1	−0.2859 (3)	0.1528 (3)	−0.5075 (2)	4.70 (7)	H4	−0.644 (3)	−0.605 (3)	0.293 (3)	5.8 (8)
C1	−0.3562 (3)	−0.4224 (3)	0.1995 (3)	3.52 (7)	H5	−0.463 (3)	−0.659 (3)	0.119 (3)	7.2 (9)
C2	−0.4633 (3)	−0.3891 (3)	0.3043 (3)	4.17 (8)	H6	−0.291 (3)	−0.544 (3)	0.056 (3)	5.9 (8)
C3	−0.5680 (3)	−0.4598 (3)	0.3405 (3)	4.95 (9)	H9A	−0.043 (3)	−0.504 (3)	0.311 (2)	4.7 (7)
C4	−0.5700 (3)	−0.5590 (3)	0.2694 (3)	5.25 (9)	H9	−0.209 (3)	−0.485 (2)	0.360 (2)	4.0 (6)
C5	−0.4686 (4)	−0.5897 (3)	0.1641 (3)	5.42 (9)	H10A	−0.146 (3)	−0.408 (3)	0.526 (3)	6.3 (8)
C6	−0.3619 (3)	−0.5224 (3)	0.1305 (3)	4.74 (8)	H10B	−0.073 (4)	−0.309 (3)	0.439 (3)	8 (1)
C7	−0.2380 (3)	−0.3524 (3)	0.1572 (3)	3.30 (7)	H10	−0.247 (3)	−0.295 (3)	0.464 (3)	8 (1)
C8	−0.1397 (3)	−0.3569 (3)	0.2236 (3)	3.38 (7)	H12	−0.172 (3)	−0.092 (3)	0.175 (3)	5.7 (8)
C9	−0.1332 (3)	−0.4377 (3)	0.3427 (3)	4.06 (7)	H13	0.003 (3)	0.016 (3)	0.119 (3)	5.9 (8)
C10	−0.1495 (4)	−0.3584 (4)	0.4541 (3)	5.46 (9)	H14	0.244 (4)	−0.091 (3)	0.088 (3)	8 (1)
C11	−0.0276 (3)	−0.2809 (3)	0.1852 (3)	3.62 (7)	H15	0.325 (3)	−0.321 (3)	0.126 (3)	7.4 (9)
C12	0.1151 (3)	−0.3415 (3)	0.1702 (3)	4.32 (8)	H16	0.141 (3)	−0.437 (3)	0.189 (3)	5.8 (8)
C13	0.2198 (3)	−0.2708 (3)	0.1342 (3)	5.17 (9)	H18	−0.440 (2)	−0.187 (2)	0.069 (2)	3.1 (6)
C14	0.1796 (4)	−0.1381 (4)	0.1154 (3)	5.98 (9)	H19	−0.457 (3)	−0.082 (3)	−0.130 (3)	5.1 (7)
C15	0.0402 (4)	−0.0751 (3)	0.1337 (3)	5.56 (9)	H21	−0.027 (3)	−0.264 (3)	−0.246 (3)	5.1 (7)
C16	−0.0659 (3)	−0.1455 (3)	0.1684 (3)	4.55 (8)	H22	−0.037 (2)	−0.359 (2)	−0.045 (2)	3.3 (6)
C17	−0.2365 (3)	−0.2853 (3)	0.0326 (3)	3.33 (6)	H23A	−0.417 (5)	−0.086 (5)	−0.338 (5)	15 (2)
C18	−0.1150 (3)	−0.3058 (3)	−0.0632 (3)	3.92 (7)	H23	−0.394 (3)	0.052 (3)	−0.300 (3)	8 (1)
C19	−0.1153 (3)	−0.2470 (3)	−0.1773 (3)	4.24 (8)	H24A	−0.210 (4)	−0.053 (4)	−0.542 (4)	11 (1)
C20	−0.2357 (3)	−0.1628 (3)	−0.2035 (3)	4.10 (7)	H24	−0.396 (4)	0.029 (3)	−0.538 (3)	8 (1)
C21	−0.3599 (3)	−0.1407 (3)	−0.1121 (3)	4.33 (8)	H25B	−0.167 (4)	0.136 (4)	−0.369 (3)	10 (1)
C22	−0.3578 (3)	−0.2037 (3)	0.0043 (3)	4.01 (7)	H25A	−0.150 (4)	0.262 (4)	−0.491 (4)	11 (1)
C23	−0.3437 (4)	−0.0297 (4)	−0.3569 (4)	6.6 (1)	H25	−0.079 (4)	0.101 (4)	−0.520 (4)	10 (1)
C24	−0.3026 (4)	0.0171 (4)	−0.4925 (3)	6.0 (1)	H26B	−0.388 (4)	0.191 (4)	−0.654 (4)	12 (1)
C25	−0.1553 (4)	0.1626 (4)	−0.4713 (4)	6.8 (1)	H26A	−0.190 (4)	0.142 (3)	−0.696 (3)	8 (1)
C26	−0.2806 (4)	0.1980 (4)	−0.6371 (4)	6.7 (1)	H26	−0.290 (4)	0.289 (4)	−0.639 (3)	10 (1)
				3-OH-T					
O1	0.0505 (1)	0.3187 (4)	0.46899 (8)	4.30 (5)	H2	0.1679	0.3811	0.4022	
O2	0.5728 (1)	0.3404 (4)	0.45590 (8)	4.33 (5)	H4	−0.0264	−0.0616	0.4467	
N1	0.7880 (2)	0.4524 (5)	0.48028 (9)	3.60 (6)	H5	0.0058	−0.3260	0.3816	
C1	0.1508 (2)	0.0824 (5)	0.3589 (1)	2.79 (6)	H6	0.1188	−0.2345	0.3260	
C2	0.1328 (2)	0.2322 (5)	0.3976 (1)	2.84 (6)	H91	0.0884	0.2590	0.2158	
C3	0.0685 (2)	0.1784 (6)	0.4301 (1)	3.10 (6)	H92	0.0582	0.1176	0.2646	
C4	0.0215 (2)	−0.0250 (6)	0.4237 (1)	3.63 (7)	H12	0.2055	0.5061	0.2061	
C5	0.0402 (2)	−0.1745 (6)	0.3861 (1)	4.04 (7)	H13	0.3269	0.6167	0.1574	
C6	0.1050 (2)	−0.1223 (6)	0.3534 (1)	3.66 (7)	H14	0.4665	0.3969	0.1638	
C7	0.2223 (2)	0.1490 (5)	0.3258 (1)	2.86 (6)	H15	0.4827	0.0590	0.2144	
C8	0.2025 (2)	0.1636 (5)	0.2728 (1)	2.99 (6)	H16	0.3646	−0.0418	0.2659	
C9	0.1056 (2)	0.1268 (6)	0.2406 (1)	3.90 (7)	H18	0.3250	0.5284	0.3298	
C10	0.0994 (2)	−0.0851 (7)	0.2061 (1)	4.74 (8)	H19	0.4732	0.6192	0.3852	
C11	0.2763 (2)	0.2254 (5)	0.2410 (1)	3.21 (6)	H21	0.4796	−0.0169	0.4527	
C12	0.2658 (2)	0.4120 (7)	0.2087 (1)	5.25 (8)	H22	0.3292	−0.0975	0.3991	
C13	0.3355 (3)	0.4756 (7)	0.1810 (1)	5.89 (9)	H231	0.5692	0.6737	0.4643	
C14	0.4146 (2)	0.3480 (7)	0.1836 (1)	5.30 (9)	H232	0.6265	0.5895	0.4185	
C15	0.4247 (2)	0.1592 (7)	0.2137 (1)	5.40 (9)	H241	0.6943	0.4958	0.5290	
C16	0.3558 (2)	0.0971 (6)	0.2424 (1)	4.14 (7)	H242	0.7234	0.7270	0.5020	
C17	0.3155 (2)	0.2040 (5)	0.3582 (1)	2.81 (6)	H1	0.0957	0.4414	0.4707	
C18	0.3578 (2)	0.4113 (6)	0.3555 (1)	3.44 (6)	H101	0.1210	−0.2363	0.2324	
C19	0.4433 (2)	0.4646 (6)	0.3876 (1)	3.53 (7)	H102	0.1445	−0.878	0.1835	
C20	0.4880 (2)	0.3073 (6)	0.4225 (1)	3.20 (6)	H103	0.0234	−0.878	0.1835	
C21	0.4467 (2)	0.0997 (5)	0.4265 (1)	3.43 (6)	H251	0.8554	0.1464	0.4726	
C22	0.3611 (2)	0.0522 (5)	0.3949 (1)	3.31 (6)	H252	0.7304	0.1171	0.4511	
C23	0.6140 (2)	0.5550 (6)	0.4557 (1)	4.48 (8)	H253	0.7578	0.1777	0.5214	
C24	0.7060 (2)	0.5643 (6)	0.4942 (1)	4.36 (8)	H261	0.7578	0.4707	0.3984	
C25	0.7835 (3)	0.2085 (7)	0.4835 (2)	5.9 (1)	H262	0.8789	0.4707	0.425	
C26	0.8072 (3)	0.5254 (9)	0.4288 (1)	6.5 (1)	H263	0.8066	0.7343	0.4316	
				2-Me-4-OH-T					
O1	0.77008 (8)	0.5964 (1)	−0.0033 (1)	6.48 (4)	C10	1.0153 (1)	0.3854 (2)	−0.1199 (2)	7.82 (7)
O2	0.81931 (6)	0.01398 (9)	0.1862 (1)	4.82 (4)	C11	1.01539 (9)	0.2213 (1)	0.0070 (2)	3.75 (4)
N1	0.78734 (9)	−0.1695 (1)	0.1881 (2)	5.28 (5)	C12	1.0743 (1)	0.2108 (2)	0.0621 (2)	4.78 (5)
CME	0.9037 (1)	0.3954 (2)	0.2146 (2)	5.84 (6)	C13	1.1073 (1)	0.1370 (2)	0.0545 (2)	5.40 (6)
C1	0.88687 (9)	0.3833 (1)	0.0271 (2)	5.71 (4)	C14	1.0826 (1)	0.0724 (2)	−0.0105 (2)	5.20 (6)
C2	0.87411 (9)	0.4242 (1)	0.1106 (2)	4.03 (5)	C15	1.0248 (1)	0.0820 (2)	−0.0669 (2)	5.63 (6)
C3	0.8350 (1)	0.4957 (1)	0.0972 (2)	4.74 (5)	C16	0.9912 (1)	0.1552 (2)	−0.0591 (2)	4.86 (5)
C4	0.8091 (1)	0.5275 (1)	0.0026 (2)	4.50 (5)	C17	0.89890 (9)	0.2251 (1)	0.0745 (1)	3.45 (4)
C5	0.8227 (1)	0.4888 (1)	−0.0795 (2)	4.43 (5)	C18	0.93384 (9)	0.1707 (1)	0.1462 (2)	4.04 (5)
C6	0.86091 (9)	0.4175 (1)	−0.0671 (2)	4.16 (5)	C19	0.90950 (9)	0.1006 (1)	0.1859 (2)	4.05 (5)
C7	0.92534 (9)	0.3028 (1)	0.0364 (1)	3.61 (4)	C20	0.84819 (9)	0.0824 (1)	0.1531 (1)	3.67 (4)
C8	0.98013 (9)	0.3018 (1)	0.0128 (2)	3.94 (5)	C21	0.81209 (9)	0.1354 (1)	0.0811 (2)	4.15 (5)
C9	0.0100 (1)	0.3836 (2)	−0.0133 (2)	5.21 (6)	C22	0.83695 (9)	0.2059 (1)	0.0443 (2)	3.79 (4)

Table II (Continued)

atom	x	y	z	B_{eq}, Å^2	atom	x	y	z	B_{eq}, Å^2
C23	0.8554 (1)	−0.0467 (1)	0.2532 (2)	4.56 (5)	H21	0.7691 (9)	0.120 (1)	0.058 (1)	4.2 (4)
C24	0.8134 (1)	−0.1161 (2)	0.2738 (2)	5.08 (5)	H22	0.8121 (8)	0.242 (1)	−0.005 (1)	4.4 (5)
C25	0.8328 (2)	−0.2248 (2)	0.1595 (2)	7.21 (8)	H91	1.052 (1)	0.385 (1)	0.027 (2)	6.5 (6)
C26	0.7400 (2)	−0.2255 (2)	0.2115 (3)	10.4 (1)	H92	0.985 (1)	0.433 (2)	−0.001 (2)	8.6 (7)
HMe1	0.897 (1)	0.431 (2)	0.268 (2)	10.3 (9)	H101	0.967 (1)	0.378 (2)	−0.176 (2)	11.7 (9)
H1	0.749 (1)	0.608 (2)	−0.076 (2)	12 (1)	H102	1.036 (1)	0.338 (2)	−0.142 (2)	8.1 (7)
HMe2	0.891 (1)	0.332 (2)	0.225 (2)	10.1 (8)	H103	1.035 (1)	0.438 (2)	−0.129 (2)	8.7 (7)
HMe3	0.947 (1)	0.385 (2)	0.219 (2)	10.9 (9)	H231	0.872 (1)	−0.017 (1)	0.318 (2)	5.7 (5)
H3	0.826 (1)	0.526 (1)	0.162 (2)	6.6 (6)	H232	0.8911 (9)	−0.072 (1)	0.225 (2)	6.0 (5)
H5	0.8055 (9)	0.510 (1)	−0.149 (1)	5.1 (5)	H241	0.780 (1)	−0.084 (2)	0.301 (2)	7.0 (6)
H6	0.8663 (8)	0.390 (1)	−0.136 (1)	3.5 (4)	H242	0.833 (1)	−0.155 (1)	0.328 (2)	6.4 (6)
H12	1.089 (1)	0.255 (1)	0.105 (1)	5.9 (5)	H251	0.861 (1)	−0.191 (2)	0.137 (2)	10.1 (8)
H13	1.149 (1)	0.134 (1)	0.096 (2)	7.0 (6)	H252	0.854 (1)	−0.265 (2)	0.218 (2)	12 (1)
H14	1.106 (1)	0.021 (1)	−0.015 (2)	6.2 (6)	H253	0.810 (1)	−0.266 (2)	0.108 (2)	11.5 (9)
H15	1.008 (1)	0.037 (2)	−0.113 (2)	7.4 (6)	H261	0.712 (1)	−0.188 (2)	0.245 (2)	13 (1)
H16	0.950 (1)	0.163 (1)	−0.098 (2)	6.5 (6)	H262	0.718 (2)	−0.243 (2)	0.158 (2)	13 (1)
H18	0.9753 (9)	0.182 (1)	0.172 (1)	5.2 (5)	H263	0.761 (2)	−0.272 (2)	0.269 (2)	12 (1)
H19	0.9355 (8)	0.063 (1)	0.238 (1)	4.4 (4)					
				2-OH-Precursor-T					
O1	0.2600 (2)	0.6189 (1)	0.0214 (1)	4.04 (4)	H3	0.143 (2)	0.371 (2)	−0.034 (2)	4.9 (5)
O2	−0.1469 (2)	0.9460 (2)	0.1429 (2)	5.86 (5)	H04	0.371 (2)	0.726 (2)	0.128 (2)	5.6 (6)
O3	0.3542 (2)	0.5311 (2)	−0.1443 (1)	5.34 (4)	H4	0.008 (2)	0.189 (2)	0.074 (2)	5.2 (6)
O4	0.3640 (1)	0.7373 (2)	0.1963 (1)	3.94 (3)	H5	−0.026 (3)	0.227 (2)	0.268 (2)	6.3 (7)
C1	0.1621 (2)	0.5313 (2)	0.2001 (2)	3.31 (4)	H6	0.067 (2)	0.430 (2)	0.349 (2)	4.2 (5)
C2	0.1827 (2)	0.5089 (2)	0.0860 (2)	3.41 (4)	H8	0.116 (2)	0.625 (2)	0.410 (2)	3.9 (5)
C3	0.1274 (2)	0.3830 (2)	0.0408 (2)	4.09 (5)	H9A	0.323 (3)	0.535 (2)	0.353 (2)	6.3 (7)
C4	0.0497 (2)	0.2778 (2)	0.1087 (2)	4.27 (5)	H9B	0.423 (2)	0.685 (2)	0.379 (2)	5.7 (6)
C5	0.0276 (3)	0.2963 (2)	0.2201 (2)	4.56 (6)	H10B	0.367 (3)	0.560 (3)	0.546 (3)	9.7 (9)
C6	0.0834 (2)	0.4221 (2)	0.2660 (2)	4.11 (5)	H10A	0.285 (3)	0.665 (3)	0.572 (3)	10 (1)
C7	0.2161 (2)	0.6742 (2)	0.2464 (2)	3.35 (4)	H10C	0.217 (4)	0.520 (4)	0.548 (3)	14 (1)
C8	0.2152 (2)	0.6808 (2)	0.3720 (2)	3.83 (5)	H12	0.451 (3)	0.899 (3)	0.343 (2)	7.9 (8)
C9	0.3250 (3)	0.6212 (3)	0.4010 (2)	4.88 (6)	H13	0.472 (4)	1.126 (3)	0.410 (3)	11 (1)
C10	0.2959 (3)	0.5915 (3)	0.5225 (2)	7.38 (8)	H14	0.280 (4)	1.181 (3)	0.540 (3)	12 (1)
C11	0.2362 (2)	0.8203 (2)	0.4196 (2)	4.26 (5)	H15	0.036 (4)	1.000 (4)	0.592 (3)	13 (1)
C12	0.3647 (3)	0.9231 (3)	0.3916 (2)	5.56 (7)	H16	0.022 (3)	0.769 (2)	0.516 (2)	6.6 (7)
C13	0.3806 (4)	1.0503 (3)	0.4365 (2)	6.84 (8)	H18	0.276 (2)	0.908 (2)	0.143 (2)	5.8 (6)
C14	0.2701 (4)	1.0753 (3)	0.5103 (3)	7.44 (9)	N19	0.121 (2)	1.017 (2)	0.103 (2)	5.8 (6)
C15	0.1422 (4)	0.9757 (3)	0.5405 (3)	7.31 (9)	H21	−0.215 (2)	0.722 (2)	0.249 (2)	4.9 (5)
C16	0.1242 (3)	0.8469 (3)	0.4943 (2)	5.57 (7)	H22	−0.073 (2)	0.609 (2)	0.289 (2)	3.7 (5)
C17	0.1174 (2)	0.7484 (2)	0.2210 (2)	3.17 (4)	H23A	−0.337 (4)	0.893 (3)	0.251 (3)	12 (1)
C18	0.1728 (2)	0.8687 (2)	0.1675 (2)	4.21 (5)	H23B	−0.331 (3)	0.955 (3)	0.133 (2)	8.6 (8)
C19	0.0817 (3)	0.9324 (2)	0.1434 (2)	4.78 (6)	H23C	−0.331 (3)	0.791 (3)	0.131 (3)	10 (1)
C20	−0.0658 (2)	0.8775 (2)	0.1738 (2)	3.97 (5)	H24	0.163 (3)	0.559 (2)	−0.114 (2)	6.6 (7)
C21	−0.1229 (2)	0.7595 (2)	0.2297 (2)	3.74 (5)	H25A	0.513 (3)	0.606 (3)	−0.047 (2)	8.1 (8)
C22	−0.0306 (2)	0.6955 (2)	0.2521 (2)	3.55 (5)	H25B	0.555 (4)	0.514 (3)	−0.171 (3)	12 (1)
C23	−0.2997 (3)	0.8865 (3)	0.1642 (3)	7.18 (8)	H26A	0.672 (4)	0.764 (3)	−0.166 (3)	12 (1)
C24	0.2689 (2)	0.6088 (2)	−0.0962 (2)	4.11 (5)	H26B	0.568 (4)	0.710 (3)	−0.270 (3)	11 (1)
C25	0.5055 (3)	0.5893 (3)	−0.1341 (3)	6.96 (8)	H27A	0.495 (3)	0.835 (3)	−0.051 (2)	7.4 (7)
C26	0.5708 (3)	0.7235 (4)	−0.1864 (3)	7.69 (9)	H27B	0.520 (3)	0.899 (3)	−0.171 (2)	7.6 (8)
C27	0.4845 (3)	0.8138 (3)	−0.1323 (2)	6.03 (7)	H28A	0.267 (3)	0.808 (3)	−0.092 (2)	7.4 (7)
C28	0.3262 (3)	0.7487 (2)	−0.1379 (2)	4.77 (6)	H28B	0.319 (2)	0.751 (2)	−0.213 (2)	5.5 (6)

Table III. Comparison of Dihedral Angles in Various Tamoxifen Structures

Atoms Defining the Planes:	
plane 1	C1, C2, C3, C4, C5, C6
plane 2	C11, C12, C13, C14, C15, C16
plane 3	C17, C18, C19, C20, C21, C22

Dihedral Angles, deg

	2-OH-T	3-OH-T	2-Me-4-OH-T	2-OH-precursor T	T
plane 1/2	56.6	60.2	49.9	48.3	59.0
plane 1/3	91.9	93.6	96.6	91.0	87.0
plane 2/3	58.0	57.0	62.2	55.1	57.0

angles (Table V) around the C7–C1 bond, for example by angles C2–C1–C7–C8 and C6–C1–C7–C8. These show that the two orientations of the substituted phenyl ring are related by an ~180° rotation, between 2-hydroxytamoxifen on the one hand and 3-hydroxy- and 2-methyl-4-hydroxytamoxifen on the other. Relations between these orientations are discussed below.

The structure of the synthetic precurson to 2-hydroxytamoxifen (Figures 4 and 5) shows that the central substituted ethane group has its attached hydrogen atom and hydroxy group in a trans orientation with respect to each other; thus, their elimination is a trans one, resulting in formation of solely the *trans*-tamoxifen.[1] The geometry of the intermediate is stabilized by an intramolecular hydrogen bond between the hydroxy group (as donor) and the ether oxygen atom O1 bridging to the tetrahydropyran ring. The O2···O1 and H···O1 distances are 2.64 and 1.95 Å, respectively, and the O2–H···O1 angle is 140°. The tetrahydropyran ring adopts an unexceptional boat conformation.

Conformation Energy Calculations. Examination of the energetics of rotation about the C1–C7 bond for both 2- and 3-hydroxytamoxifen (Figure 6) shows that free rotation is not possible. Two principal equienergy minima are seen, corresponding to the two categories of orientation found in the crystal structures. The barrier between them is so high (>999 kcal mol^{-1}) that they are not interconvertible, at least on the basis of pure C1–C7 bond rotation.

Table IV. Selected Bond Lengths (Å) and Angles (deg)

	2-OH-T	3-OH-T	2-Me-4-OH-T	2-OH-precursor-T
		Distances		
C1–C2	1.393	1.394	1.398	1.399
C1–C6	1.384	1.386	1.397	1.391
C1–C7	1.495	1.505	1.503	1.544
C2–C3	1.386	1.393	1.397	1.391
C2–O2	1.368			
C2–CMe			1.498	
C3–C4	1.378	1.388	1.387	1.373
C3–O3		1.362		
C4–C5	1.366	1.376	1.375	1.363
C4–O4			1.369	
C5–C6	1.379	1.400	1.382	1.395
C7–C8	1.342	1.339	1.351	1.552
C7–C17	1.494	1.490	1.486	1.539
C8–C9	1.514	1.511	1.511	1.545
C8–C11	1.489	1.503	1.486	1.517
av esd	0.004	0.004	0.003	0.004
		Angles		
C2–C1–C6	117.3	119.4	118.2	117.0
C2–C1–C7	123.1	117.7	121.8	119.6
C6–C1–C7	119.6	122.8	119.9	123.2
C1–C2–C3	120.4	120.4	119.4	121.4
C2–C3–C4	120.4	119.8	121.2	119.9
C3–C4–C5	119.9	119.8	119.5	120.2
C4–C5–C6	119.4	120.7	119.7	120.2
C1–C6–C5	122.3	119.7	121.9	121.3
C1–C7–C8	122.9	122.9	122.2	113.6
C1–C7–C17	113.8	113.0	115.0	107.1
C8–C7–C17	123.2	124.0	122.8	109.9
C7–C8–C9	122.7	123.7	122.2	112.2
C7–C8–C11	122.6	121.4	123.7	112.2
C9–C8–C11	114.7	114.9	114.1	111.5
av esd	0.2	0.3	0.2	0.2

Table V. Selected Torsion Angles (deg)

	2-OH-T	3-OH-T	2-Me-4-OH-T	2-OH-precursor-T
C2–C1–C7–C17	−117.6	56.1	64.8	70.6
C2–C1–C7–C8	65.8	−121.9	−114.4	−167.8
C6–C1–C7–C8	−115.5	60.2	67.8	−16.0
C1–C7–C8–C9	3.5	3.2	7.1	66.3
C1–C7–C17–C22	49.7	54.3	40.1	53.0
C7–C8–C9–C10	−119.9	−112.0	−113.7	−163.7
C7–C8–C11–C12	−124.9	−120.7	−124.1	−66.7
O2–C23–C24–N1	−100.0	74.1	67.1	
C23–C24–N1–C25	72.6	54.3	68.8	
av esd	0.4	0.3	0.3	0.3

The energy wells, though steep, are quite broad; in the case of the one centered at ~260° for the C6–C1–C7–C8 torsion angle, there is about ±25° flexibility. This steric hindrance to rotation was further shown by a molecular graphics study of the close contacts produced upon rotation around the C1–C7 bond. At the observed torsion angle of 60.2° for the C6–C1–C7–C8 group of 3-hydroxytamoxifen, the nonbonded distances H2···H22 and H6···H92 were 3.70 and 2.68 Å, respectively. When the torsion angle was altered to 0°, these distances became 1.90 and 1.04 Å, respectively, which necessarily produce a highly repulsive intramolecular energy. These distances are too short to be even in part compensated by 5–7° bond angle changes. The 2-methyl-4-hydroxy compound has a very similar energy profile for rotation about the C1–C7 bond. The 60–80° minimum is narrower in this case, probably on account of the increase in repulsive close contacts with the ethyl group, when the 2-hydroxy substituent is replaced by the more bulky 2-methyl one. The observed orientation for the 2-hydroxy derivative may derive small additional stabilization from a C–H···O interaction between the 2-hydroxy group and C–H group on the terminal methyl.

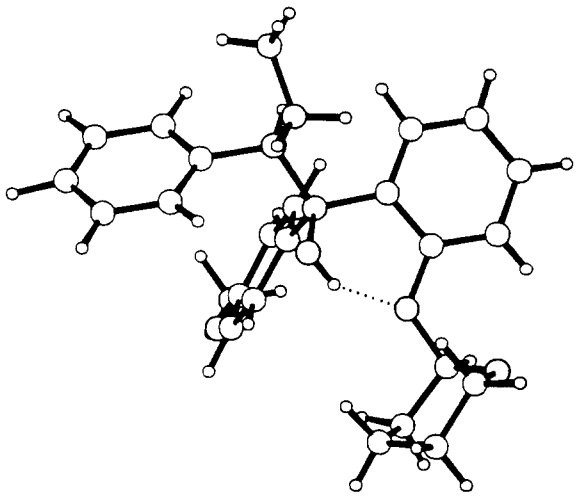


Figure 5. View of the synthetic precursor, showing the intramolecular hydrogen bond (as dashed line).

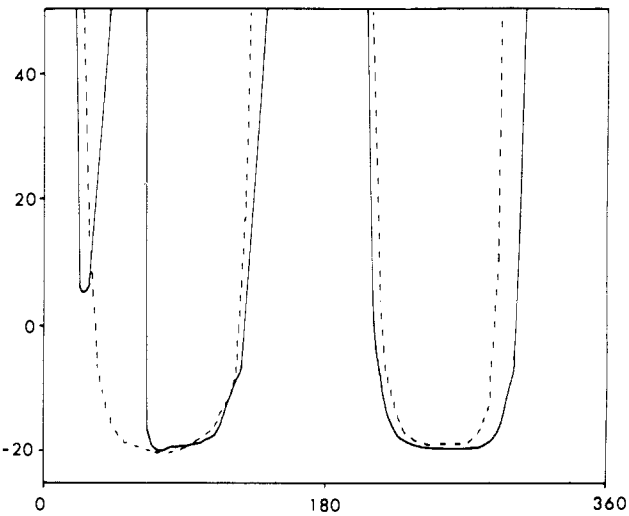


Figure 6. Energy plots for rotation about the C6–C1–C7–C8 bond, for 2-hydroxytamoxifen (shown as dashed lines) and 3-hydroxytamoxifen. The horizontal axis shows the C6–C1–C7–C8 torsion angle (deg). The vertical axis shows nonbonded intramolecular energy (kcal mol^{-1}).

The C–H···O angles is 132°, and the H···O distance is 2.56 Å; these dimensions indicate that the atoms are just within van der Waals separation.

Each of the three hydroxylated tamoxifens can thus exist in principle as two noninterconvertible stereoisomers. The structures found in the crystal may then be the result of either isomer resolution by crystallization or stereospecific synthesis. The latter possibility seems more likely since no chemical indication of two isomers has been observed.[1]

The noninterconvertibility of potential rotamers about the C1–C7 bond is further shown by two-dimensional energy plots where rotations about both this and another ethylene substituent are examined. In general, virtually identical plots have been obtained for three hydroxylated tamoxifens and the discussion below is applicable to all. Figure 7 shows rotation about the C1–C7 and C7–C17 bonds for 3-hydroxytamoxifen. Four symmetrically disposed low-energy domains are observed, with the experimentally determined 3-hydroxy conformation occurring in one of these and being within 1 kcal mol^{-1} of the global energy minimum. The 2-hydroxy energy map is essentially identical, and in this case the observed conformation is at the global energy minimum. The four low-energy domains are energetically noninterconvertible, with barriers >999

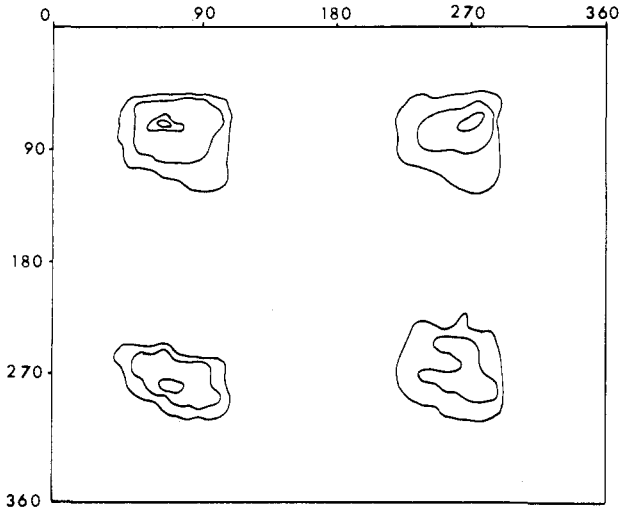


Figure 7. Two-dimensional energy plot for 3-hydroxytamoxifen. The horizontal axis designates increments for the C1–C7–C17–C22 torsion angle, and the vertical corresponds to the C2–C1–C7–C8 torsion angle. Contours are drawn at 1 kcal mol^{-1} intervals.

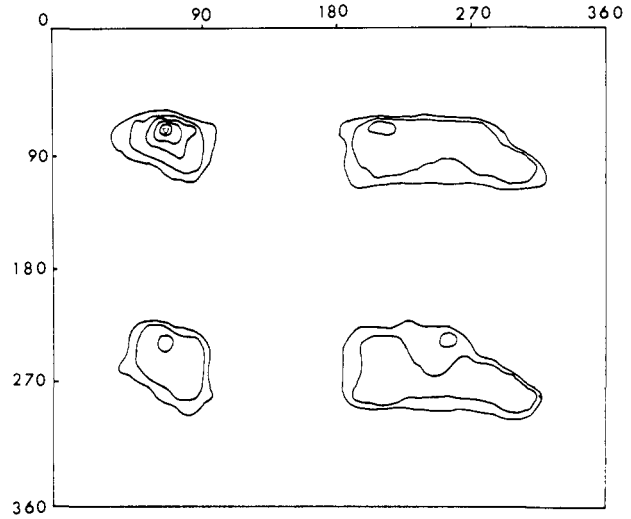


Figure 8. Two-dimensional energy plot for 3-hydroxytamoxifen, with rotation about C7–C8–C9–C10 along the horizontal axis and about the C6–C1–C7–C8 torsion angle along the vertical axis. Contours are drawn at 1 kcal mol^{-1} intervals, and the global minimum is indicated by ▽.

kcal mol^{-1}. Rotation around C1–C7 with respect to the ethyl substituent has also been examined. Figure 8 is with respect to the C8–C9 bond. Again, four low-energy domains are found in the energy map, and the observed conformation occurs in a domain that is some 1.5 kcal mol^{-1} higher than the global minima. The two domains centered around a value of 250° for the C7–C8–C9–C10 torsion angle have a broad minima for this angle, indicating that the terminal $-CH_3$ part of the ethyl group has some flexibility; this is qualitatively apparent from careful consideration of the space-filling plots in Figures 1-3. Energy minimization about the C1–C7, C8–C9, C8–C11, and C7–C17 bonds for the 3-hydroxy derivative indicated that the observed conformation with respect to these four bonds was within a minimum energy position. Thus, the total energy diminished by only 0.5 kcal mol^{-1}, and the torsion angle changes were all within the limits indicated by the domains in the two-angle plots.

The conformational relationships of the (dimethylamino)ethoxy side chain have also been examined (Figure 9). This shows that the three principle conformations about the N–C–C–O bond are of ~1 kcal mol^{-1} difference and that the barriers between them are only a few kcal mol^{-1}. There are three low-energy domains for rotation about the C24–N1 bond, viz. gauche$^+$, trans, and gauche$^-$. The first two are separated by a low-energy barrier whereas the gauche$^-$ conformation is more distinct. The observed conformations all fall within the slightly preferred gauche$^+$ range.

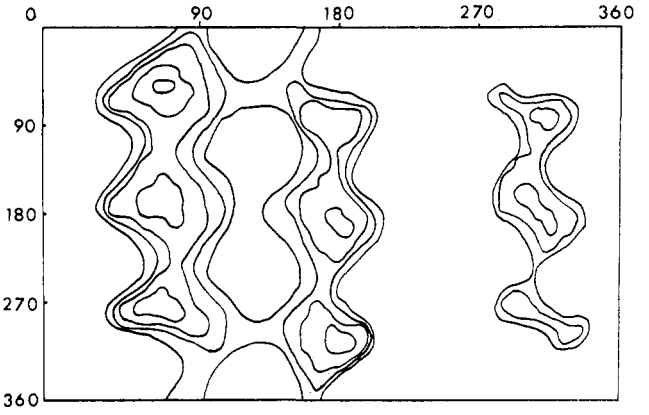


Figure 9. Two-dimensional energy plot for the (dimethylamino)ethoxy side chain (in 3-hydroxytamoxifen). The horizontal axis corresponds to increments of the C23–C24–N1–C25 torsion angle and the vertical to the O2–C23–C24–N1 angle. Contours are drawn at 1 kcal mol^{-1} intervals.

Relationships to Biological Activity. The accompanying paper[1] provides data on the relative binding affinities (RBA) to the estrogen receptor for various tamoxifen derivatives. The 2-methyl-4-hydroxy derivative has a 100-fold times greater RBA than tamoxifen itself, whereas the 2-hydroxy RBA is 10 times less than tamoxifen. Hydroxylation at the 3-position results in a modest increase in RBA compared to tamoxifen. Assuming that the conformations found in the crystal structure analyses reported here are indeed those of the compounds administered for assay, it is possible to draw some general conclusions concerning the nature of their estrogen receptor binding site. The fact that the RBA is considerably diminished when a hydroxy group is on the "top" face of the molecule (Figure 1) suggests that this face is important for binding and that this region of the molecule is required to be hydrophobic in nature. The importance of this face is reinforced by the enhanced RBA when either a hydrophobic methyl group (in the 2-methyl-4-hydroxy derivative) or a hydrophilic hydroxy group (in the 3-hydroxy derivative) is on the "rear" face (Figures 2 and 3). This reasoning is supported by results in the previous paper. This implies that the nature of the substitution on this side is of lesser importance and thus may not be in critical contact with the receptor binding site. The 4-hydroxylation is clearly of major importance for high RBA, indicating a possible hydrogen-bonding interaction at this point of the receptor site.

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Registry No. 2-Hydroxytamoxifen, 97135-08-5; 3-hydroxytamoxifen, 83647-29-4; 2-methyl-4-hydroxytamoxifen, 97135-09-6; 1-(4-methoxyphenyl)-1-[2-(tetrahydropyran-2-yloxy)phenyl]-2-phenyl-1-butanol, 97135-10-9.