benzylic CH_2 and equatorial N_1 CH), 3.1–4.1 (2 m, 2 H, axial N_1 CH and axial N_2 CH), 6.7–7.2 (m, 7 H, aryl H). The oil was dissolved in 20 mL of dry Et_2O and a solution of 20 mL of Et_2O saturated with HCl gas was added dropwise to precipitate the hydrochloride salt as a yellow powder. The powder was recrystallized from MeOH to give 580 mg (67%) of rhombic crystals, mp 121 °C dec. Anal. ($C_{18}H_{20}N_2S$·HCl) C, H, N, S.

[^{3}H]Spiperone Binding. Binding experiments were carried out in twice washed 5% homogenates obtained from rat corpus striatum (or frozen calf caudate). Male, Sprague–Dawley rats (150–300 g) were decapitated, and their brains were immediately removed and dissected. The brain tissue was weighed and then homogenized in ice-cold 0.05 M sodium–potassium phosphate buffer (pH 7.4). After centrifugation at 48000*g* for 20 min (Sorvall RC2-B), the supernatant was discarded, the pellet was resuspended in distilled water, and the process was repeated. The final pellet was resuspended in 50 volumes of ice-cold 0.05 M Tris buffer (pH 7.4). Aliquots of brain tissue (final concentration 1.25 mg/mL), [^{3}H]spiperone (100 pM), and drugs (1, promazine hydrochloride and chlorpromazine hydrochloride) were incubated in buffer (final assay volume 2 mL) for 30 min at 37 °C. The binding reaction was terminated by filtration in vacuo over Whatman GF/B filters and rinsing with 3 × 5 mL of ice-cold buffer. Tissue radioactivity was extracted overnight in 6 mL of scintillation fluid [1 L of toluene (Baker), 1 L of Triton X-100 (NEN), 16 g of Omnifluor (NEN)] and measured in a Searle Mark II liquid scintillation counter (45% efficiency). Specific [^{3}H]-spiperone binding was defined as the difference between binding in the absence and in the presence of 1 μM (+)-butaclamol. The negative logarithm of the concentration of drug producing a 50% inhibition of specific binding (pIC_{50}) values were estimated graphically from logarithmic Hill plots composed of at least five points on the decline of the curve and converted to IC_{50} values.

Homovanillic Acid (HVA) Increase in Rat Corpus Striatum. The hydrochloride salt of 1 was dissolved in a 10% PEG 400 solution in distilled water. Promazine hydrochloride was dissolved in distilled water. Female Wistar rats (140–180 g) were injected ip with the drug solution or saline (controls). The rats were decapitated 2 h after the injections, and the corpus striatum was dissected on a cold plate, immediately frozen in liquid nitrogen, weighed, and homogenized in 1 mL of 0.4 M perchloric acid. After addition of KOH/potassium formate solution and centrifugation (15 min, 5000*g*, 2 °C), the supernatant was assayed for HVA by its isolation on small Sephadex G columns and its conversion to a fluorophor by oxidative dimerization with $K_3Fe(CN)_6$, followed by automated fluorimetric analysis.[31]

Acknowledgment. Support in the form of PHS Research Grant MH31184 and Postdoctoral Fellowship MH07507 (to A.R.M.) from the National Institute of Mental Health is gratefully acknowledged. We also thank B. H. C. Westerink for assistance with the HVA assay.

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Crystal and Molecular Structure of Nafoxidine and Stereochemical Features of Anticancer Antiestrogens

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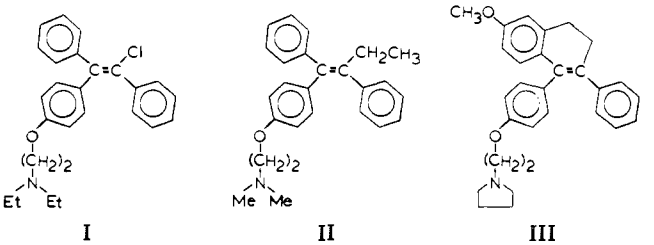
We have determined the molecular structure of the anticancer antiestrogen nafoxidine and compared its three-dimensional structure with two other clinically useful antiestrogens in order to delineate stereochemical parameters in these compounds. Crystals of nafoxidine hydrochloride–ethanol are monoclinic with cell dimensions a = 17.040, b = 7.967, c = 25.260 Å, β = 123.7°, and space group $P2_1/c$ with four formula units per cell. The structure was solved by direct phasing methods and refined to a discrepancy index of 0.068. The methoxyphenyl and phenyl rings are trans to each other relative to the ethylene bond, and the substituted amine–aryl ether chain has an extended conformation. Stereoscopic superposition drawings and tabular data are given to show structural similarities and differences in nafoxidine, clomiphene, and tamoxifen, the three antiestrogens with demonstrated clinical efficacy in the management of metastatic mammary carcinoma.

Breast cancer is the most common malignancy among North American and European women. Therapeutic management is an important problem, as about two-thirds of all patients eventually require treatment for disseminated disease. Hormonal manipulation has conventionally been the mainstay of therapy in this phase; however, only about one-third of patients show clinical response, and endocrine control is often temporary. In recent years the prospects for management of metastatic breast cancer have improved through (1) the identification of estrogen receptors (ER) in 50–65% of breast tumors and the predictive use of this test for potential response to hormonal therapy and (2) the development of nonsteroidal antiestrogens for use with patients with ER-positive tumors.[1]

Three antiestrogens with consistent activity in human breast cancer have been identified: Clomiphene (I) was



I II III

the first antiestrogen to show clinical usefulness,[2] but it has not been widely tested and is not currently approved for this use. Tamoxifen[3] (II) has recently been marketed after extensive trials; clinical results show it to be at least as effective as hormone treatment, with much reduced side effects. Nafoxidine (III) was originally synthesized[4] as an

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Table I. Final Positional Parameters (Fractional) × 10^4 and Standard Deviations

atom	x	y	z	atom	x	y	z
Cl	4403(1)	3319(2)	497(1)	C18	6838(4)	3451(8)	934(2)
C1	8030(4)	5199(7)	3821(2)	C19	7086(4)	3004(8)	456(2)
C2	7685(4)	6623(8)	3900(3)	N20	6219(3)	3019(6)	-207(2)
C3	7805(4)	6941(8)	4537(3)	C21	6455(5)	2663(9)	-701(3)
C4	8746(5)	6241(8)	5089(3)	C22	5617(7)	1773(13)	-1210(4)
C5	9172(4)	3189(9)	5439(3)	C23	4922(5)	1494(10)	-1047(3)
C6	9227(5)	1547(9)	5305(3)	C24	5466(4)	1772(9)	-331(3)
C7	8930(5)	1056(8)	4695(3)	C25	7166(4)	7943(8)	3411(3)
C8	8568(4)	2241(8)	4214(3)	C26	6323(5)	8567(9)	3300(3)
C9	8811(4)	4398(8)	4962(3)	C27	5820(5)	9836(10)	2849(3)
C10	8489(4)	3929(8)	4332(3)	C28	6175(6)	10545(9)	2524(3)
C11	7922(4)	4759(8)	3196(3)	C29	7021(6)	9937(10)	2638(3)
C12	7041(4)	4708(8)	2626(3)	C30	7512(5)	8635(8)	3071(3)
C13	6941(4)	4288(7)	2050(2)	O31	9538(4)	260(6)	5744(2)
C14	7742(4)	3960(7)	2058(3)	C32	9842(5)	639(11)	6376(3)
C15	8632(4)	3979(8)	2620(3)	C33	2343(8)	2910(15)	3756(5)
C16	8707(4)	4381(8)	3187(3)	C34	1537(8)	3762(16)	3264(5)
O17	7738(3)	3562(5)	1521(2)	O35	2790(5)	3810(8)	4294(3)

antifertility agent; its potential value in the treatment of breast cancer was soon recognized.[5] It has also been extensively studied and, although still investigational, appears to be similar in effectiveness to the others.

Although the modes of action of these compounds have not been definitively established, there are indications that they bind to the cytoplasmic ER and are transported to the cell nucleus. We have determined the crystal and molecular structure of nafoxidine and present here details of its three-dimensional structure and quantitative comparisons with the structures of clomiphene and tamoxifen. A knowledge of stereochemical similarities and variabilities in these clinically valuable antiestrogens may be useful in the rational development of additional agents with increased ER binding capabilities.

Experimental Section

Nafoxidine [1-(*p*-2-pyrrolidinethoxyphenyl)-2-phenyl-3,4-dihydro-6-methoxynaphthalene] hydrochloride (NSC 70735) was supplied by the Developmental Therapeutics Program, Chemotherapy, NCI, and colorless crystals were obtained from absolute ethanol. The structure determination revealed the presence of 1 mol of ethanol per mole of nafoxidine hydrochloride in the cell.

Crystal Data [λ(Cu Kα) = 1.541 78 Å] for nafoxidine hydrochloride–ethanol: $C_{28}H_{32}NO_2Cl{\cdot}CH_3CH_2OH$, formula weight 508.1; monoclinic, a = 17.040(5), b = 7.967(3), c = 25.260(9) Å, β = 123.7(2)°, U = 2853.0 Å^3, d_x 1.18 g/cm^3, Z = 4, space group $P2_1/c$; μ(Cu Kα) = 14.1 cm^{-1}.

A small plate-shaped crystal, 0.07 × 0.23 × 0.31 mm, was chosen and the X-ray intensities of all independent reflections having 2θ(Cu Kα) < 130° were measured on an automated four-circle diffractometer using nickel-filtered Cu Kα radiation and the 2θ–θ scan technique. The intensities were corrected for background, and structure amplitudes were derived in the usual way. No absorption corrections were applied. A total of 4857 unique reflections were measured, of which 2188 were considered to be observed [$I > 3\sigma(I)$] and were used in the structure refinement.

Structure Determination and Refinement. The structure was solved using the direct phasing progam MULTAN 78. Input was 251 reflections with $|E| > 1.80$, and the E map based on the best set of phases allowed identification of probable positions of 33 atoms (R = 0.45). A difference Fourier distribution indicated shifts for two of the atoms and unambiguous identification of the chloride ion; one cycle of isotropic least-squares refinement dropped the discrepancy factor R to 0.20. A further difference map revealed an ethanol molecule per mole of nafoxidine. Alternating cycles of anisotropic least-squares refinement (R = 0.10) followed by difference maps led to the positions for all hydrogen atoms except for two of the ethanol molecule's methyl group. Final refinement, including hydrogen positions but not temperature factors (fixed at B = 7.0 Å^2), resulted in R = 0.068 for the observed reflections. The maximum shift/error in the final cycle was 0.44 (average = 0.10), the final $[\Sigma\omega(F_o - F_c)^2/(m-n)]^{1/2}$ = 1.0, weights ω being derived from counter statistics. Scattering factors were as cited for the real[6] and imaginary[7] components. Table I lists the fractional coordinates for the nonhydrogen atoms; anisotropic thermal parameters, hydrogen atom coordinates, and tables of the observed and calculated structure factors are available.[8]

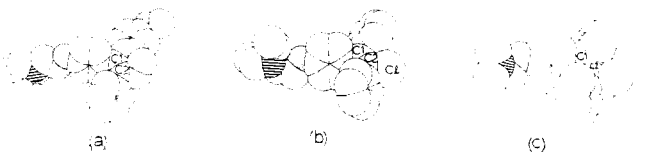

Figure 1. Space-filling representations of the three-dimensional structures of the anticancer antiestrogens, plotted from crystal structure coordinates: (a) nafoxidine, (b) clomiphene, (c) tamoxifen. Dotted atoms = oxygen, striped atoms = nitrogen, unlabelled atoms = carbon. Hydrogen atoms have been omitted for clarity.

Results and Discussion

A. Description of the Structure. The structure and conformation of nafoxidine hydrochloride are shown in Figure 1a, which is a space-filling plot constructed from the crystal structure coordinates. The atomic numbering scheme and bond lengths and angles in the molecule are given in Figure 2.

As expected from structure determinations of related compounds,[9,10] the phenyl rings (methoxyphenyl and phenyl in nafoxidine) are trans to each other relative to the ethylenic double bond in nafoxidine; this structural feature appears to be necessary for antiestrogenic activity. All three aromatic rings in the molecule are planar (maximum atomic deviation from the plane is 0.01 Å); the central partially unsaturated ring (C1–C2–C3–C4–C9–C10)

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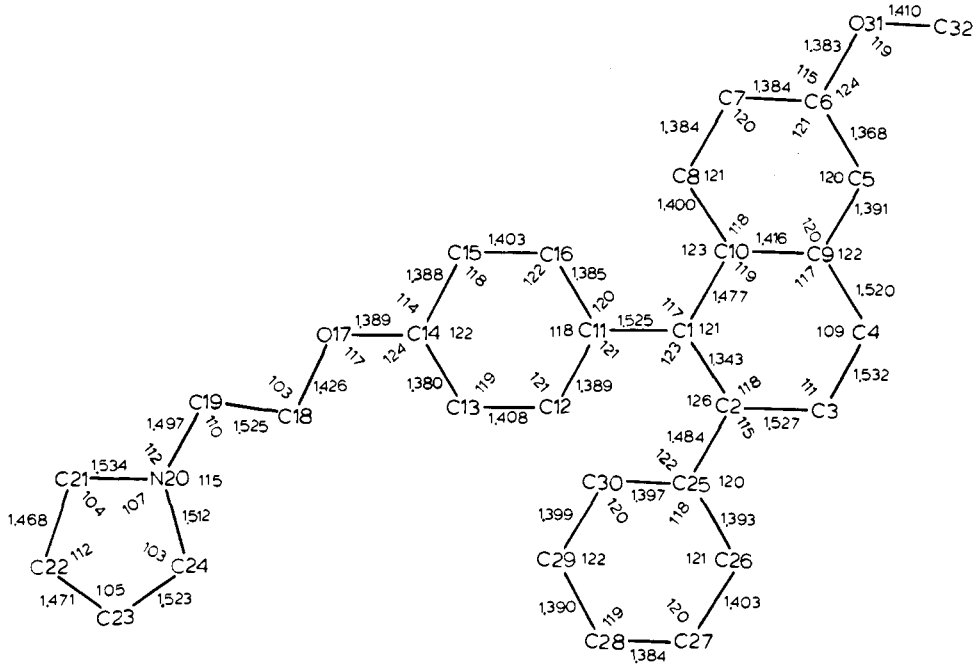

Figure 2. Atomic numbering scheme and bond lengths (Å) and angles (deg) in nafoxidine hydrochloride. Standard deviations are 0.006–0.009 Å and 0.5–0.7°.

is best described as a half-chair, with C3 and C4 on opposite sides of the (approximate) plane of the other atoms. The aryl ether substituted amine entity on C1 adopts an extended configuration; the conformation of the five-membered heterocycle is an envelope, with C24 lying 0.48 Å out of the N(20)–C(21)–C(22)–C(23) plane.

The bond lengths and angles in nafoxidine hydrochloride are normal. The value of 1.343 Å for C1–C2 is indicative of a double bond, while the lengths and angles at C3 and C4 confirm their saturated character. The nitrogen atom (N20) is protonated in nafoxidine hydrochloride, and this is reflected in the bond lengths and near-tetrahedral values of the angles around the nitrogen. There are two hydrogen bonds formed in the structure, both involving the chloride ion. One hydrogen is donated by the protonated N20 (N^+–H = 1.11 Å, N^+···Cl^- = 3.05 Å, H···Cl^- = 2.01 Å, N^+–H···Cl^- = 155°), while the other proton donor is the hydroxyl group of the ethanol molecule (O–H = 0.99 Å, O···Cl^- = 3.22 Å, H···Cl^- = 2.44 Å, O–H···Cl^- = 135°). All other intermolecular contacts correspond to normal van der Waals separations.

B. Comparisons with Other Antiestrogens. The three-dimensional structure of clomiphene (I) hydrochloride has been determined;[10] a space-filling model constructed from the atomic coordinates is shown in Figure 1b. The crystal structure of the other clinically effective anticancer antiestrogen, tamoxifen (II), has also very recently been elucidated,[9] and the molecular structure is depicted in Figure 1c. It is clear from Figure 1 that there is a high degree of conformational similarity maintained in the three molecules in their respective crystal structures: the aromatic rings have similar mutual orientations, and the orientation of the ethoxy chain with respect to its phenyl ring is the same in each.

The stereochemistries of the three antiestrogens are compared graphically in Figure 3 and numerically in Table II. As can be seen from Figure 3a and Table II, the conformations of the triarylethylene portions of clomiphene and tamoxifen are virtually identical. The torsion angles describing the R_2–N^+–C–C–O–Ar chain are also similar in the two structures; the conformation of the O–C–C–N^+ system is gauche and the small difference in

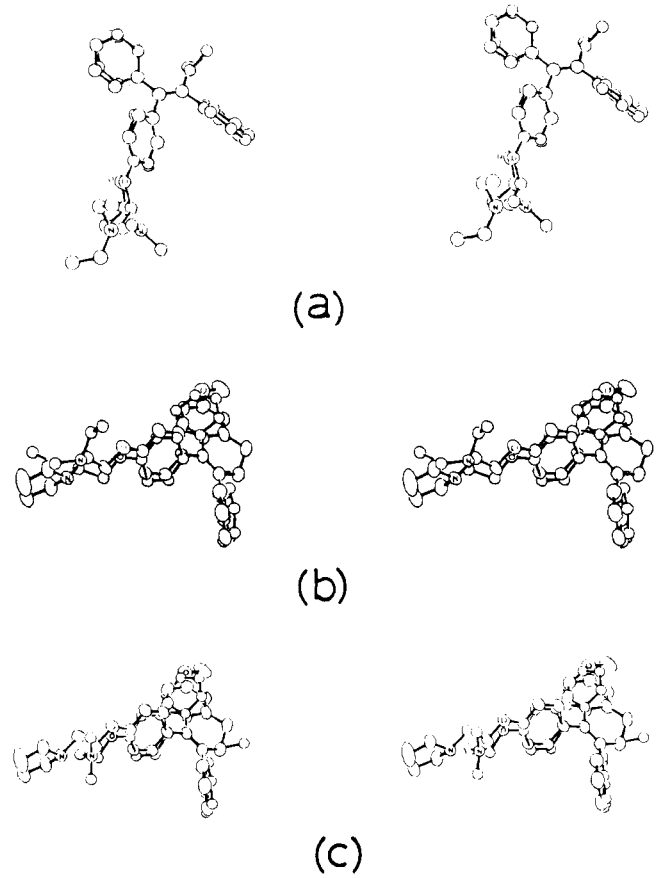

Figure 3. Stereoscopic drawings of superposed structures of the anticancer antiestrogens: (a) clomiphene and tamoxifen, (b) clomiphene and nafoxidine, (c) tamoxifen and nafoxidine.

the position of the nitrogens in the two is insignificant considering the rotational freedom in this part of the molecule. One would expect very similar receptor-binding and pharmacological properties in these two compounds, based on the overwhelming stereochemical similarity.

Figures 3b and 3c illustrate superpositions of the structure of nafoxidine and clomiphene and tamoxifen,

Table II. Comparable Stereochemical Features in Anticancer Antiestrogens

feature	nafoxidine	tamoxifen	clomiphene
N···O distance (Å)	3.66	3.02	2.96
N···C=C distance	9.32	8.62	8.97
O···C=C distance	6.09	6.06	6.07
C14-O17-C18-C19 torsion angle[a]	−179.9°	173.2°	−168.1°
O17-C18-C19-N20 torsion angle[a]	−173.8°	−76.7	−66.1°
comparable angles between ring normals[b]			
R_1-R_2	112°	59°	67°
R_1-R_3	110°	87°	78°
R_2-R_3	55°	57°	65°

[a] All of the compounds crystallize as racemic mixtures; similar enantiomers were chosen for comparative analysis. [b] R_1 = phenyl (or methoxyphenyl) ring on C1; R_2 = phenyl ring on C2; R_3 = substituted amine containing aryl ether ring on C1.

respectively. In both cases, the overall conformations of the molecules are similar. The effects of formation of the fused ring system involving the C1–C2 ethylene grouping in nafoxidine are (1) a somewhat different orientation of the methoxyphenyl group in nafoxidine from the orientations of the corresponding phenyl rings in clomiphene and tamoxifen, and, more importantly, restriction of rotational freedom of the methoxyphenyl ring and (2) introduction of more rigid hydrophobic bulk between the trans phenyl ring systems. The conformation of the N^+–C–C–O chain in nafoxidine is trans, rather than gauche as in clomiphene or tamoxifen (Table II), but there is ample structural evidence that the conformation here can be quite variable and that conformational interconversion is energetically unhampered. For example, in the crystal structure of *cis*-tamoxifen[11] there are two molecules in the asymmetric unit, distinguished by trans and gauche conformations of the N^+–C–C–O chain, and a structure determination of clomiphene hydroiodide[12] revealed four independent molecules differing in torsion angles in this chain. Inspection of Figures 3b and 3c shows that even neglecting rotational freedom, the positions of the nitrogen and oxygen electron-donor functions do not differ greatly in the superposed structures. The N^+–H orientation does differ somewhat in tamoxifen from the other two structures but this is likely of little significance because (1) free rotation is possible here and (2) there is no evidence regarding the state of protonation of the nitrogen at the site of antiestrogenic action. The presence of the ring structure at the nitrogen in nafoxidine lends organization to the hydrophobic character of that end of the molecule.

It would be of great interest to be able to relate any observed differences in biological activities of nafoxidine and the other two molecules to quantitative differences in their molecular parameters, such as those given in Table II. Unfortunately, such correlations are presently premature and must await extensive comparative studies of ER binding activities, clinical efficacies, and metabolic mechanisms of these and structurally related compounds. This work describes the three-dimensional stereochemistry of nafoxidine and compares it in detail with the known structures of clomiphene and tamoxifen, the other two antiestrogens with demonstrated clinical promise in the

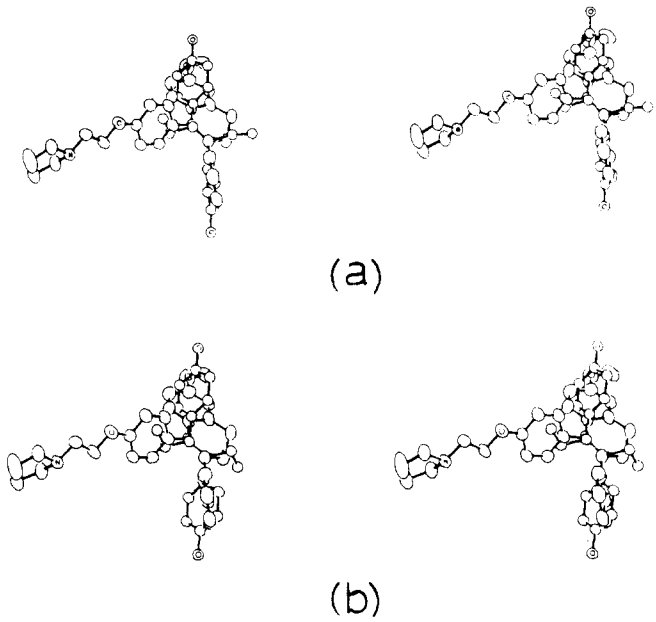

Figure 4. Stereoscopic drawings of superposed structures of nafoxidine and (a) the noncentrosymmetrical conformation and (b) the centrosymmetrical conformation of diethylstilbestrol.

hormonal management of breast cancer. The stereochemical parameters presented may be indicative of the ranges allowable with concomitant clinical usefulness; the results are presented both to establish fundamental parameters for these compounds and in the hope that they will prove useful to basic and clinical researchers.

It would also be of interest to try to identify the stereochemical features of the anticancer antiestrogens responsible for ER binding, by comparing nafoxidine (for example) structurally with structurally related estrogens, such as diethylstilbestrol (DES). There have been two solid-state conformations found for DES;[13,14] Figure 4 shows structural comparisons of nafoxidine with both of these. The asymmetrical form of DES resembles estradiol derivatives more closely than does the symmetric conformation;[15] Figure 4 shows that the *trans*-stilbene part of nafoxidine fits better with the asymmetric DES conformation as well. One might guess from this that ER binding is attributable to this part of the molecule, with antiestrogenic action perhaps conferred by participation of the side-chain functional groups in additional interactions, but more specific conclusions are clearly unwarranted. It does appear that the relatively fixed mutual positionings of the aryl groups, caused by the unsaturated central bond, is a requirement for fitting the receptor, as similar compounds having a saturated C1–C2 bond were not, on the whole, clinically useful.[16,17] Further separation and identification of the stereochemical features responsible for estrogenic and antiestrogenic properties in these molecules require extensive and detailed structural comparisons among the

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steroid estrogens and the cis and trans forms of the nonsteroidal estrogens and antiestrogens, guided by detailed knowledge of receptor-binding and biological activities of all of these molecules and specially chosen active and inactive analogues.

Acknowledgment. We thank C. Weeks for providing tamoxifen coordinates. Support of this work was from the Medical Research Council of Canada and from the NIH (Grant CA 15879).

Supplementary Material Available: A list of observed and calculated structure factors, a table of anisotropic thermal parameters, and a table of hydrogen atom positional coordinates (27 pages). Ordering information is given on any current masthead page.

Experimental Antiulcer Drugs. 4. 1,3-Disubstituted 2,4,5,6-Tetrahydro-4,6,6-trimethyl-2-phenylcyclopenta[*c*]pyrrole-4-carboxamides[1]

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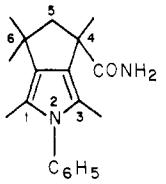
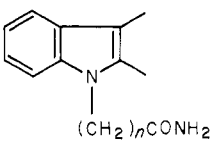
The synthesis of 1,3-disubstituted 2,4,5,6-tetrahydro-4,6,6-trimethyl-2-phenylcyclopenta[*c*]pyrrole-4-carboxamides is reported. The derivatives included $R_1 = R_3 = H$, $R_1 = CH_2OH$ with $R_3 = H$ (**16**) or CH_3, $R_1 = CH_3$ with $R_3 = CH_2OH$ (**17**), and $R_1 = R_3 = CH_2OH$. The monohydroxymethyl derivatives were as active as the parent cyclopentapyrrole, where $R_1 = R_3 = CH_3$ (**1**), when administered orally in the pyloric ligated rat. The compounds lacking one or both CH_3 groups at C-1 or C-3 were much less active. Compounds **16** and **17** inhibited histamine-induced gastric acid secretion in the dog.

The outstanding gastric antisecretory activity of the cyclopentapyrrole **1** in the rat and the dog has been reported in our previous publication.[2] Examination of the effect of varying the substituents at N-2 on the oral gastric antisecretory activity in the rat led to the conclusion that an unsubstituted phenyl group was the optimal substituent. We now report a study of the effect of varying the substituents at C-1 and C-3, in particular the effect of hydroxylation, homologation, and replacement by hydrogen of the methyl groups. The same modifications of the methyl groups in the 2,3-dimethylindole-1-alkanamide (**2**) series had demonstrated that their presence was a requirement for high oral antisecretory activity in the rat.[3]



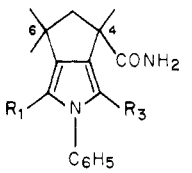
1



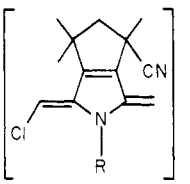
2

Chemistry. Functionalization of the C-1 and C-3 methyl groups was accomplished through chlorination with sulfuryl chloride. The chlorination products which could be prepared in good yield were the dichloro **4**, tetrachloro **19**, and pentachloro **7** derivatives (Schemes I and II). Solvolysis of the dichloro compound **4** in trifluoroacetic acid yielded a mixture of aldehydes consisting of three parts of the 3-aldehyde **5** and one part of the 1-aldehyde **6**. Pure **5** could be isolated in about 25% yield by direct crystallization. Hydration of the mixture of nitrile aldehydes yielded a mixture of aldehyde amides from which the 1-aldehyde amide **10** could be isolated in low yield. The formation of **5** and **6** may result from the occurrence of both possible modes of elimination of HCl from **4** to give the intermediates **25** and **26**. Addition of HX would give,

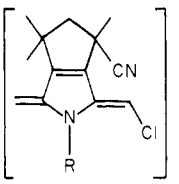
Table I. NMR Spectra of the Aldehydes in $CDCl_3$



		$\Delta\delta$ from $R_1 = R_3 = CH_3$	
R_1	R_3	C-4 CH_3	C-6 CH_3's
CH_3	CHO	−0.10	−0.03, −0.03
CHO	CH_3	−0.02	−0.18, −0.14
CHO	CHO	−0.11	−0.15, −0.17



25, R = C_6H_5



26, R = C_6H_5

respectively, the precursors to **5** and **6**. The monoaldehydes afforded the target compounds **13**, **14**, **17**, and **18** by the routes indicated in Scheme I.

The 3-unsubstituted 1-hydroxymethyl derivative **16** proved to be readily available from the pentachloro compound **7**. A noteworthy step in this sequence is the excellent decarboxylation procedure utilizing aniline in boiling dimethylaniline. This reagent combination has been reported to be effective in the decarboxylation of 3-formylindole-2-carboxylic acid.[4] The 1,3-bis(hydroxy-

(1) For Part 3, see M. R. Bell, R. Oesterlin, K. O. Gelotte, A. G. Hlavac, and A. V. R. Crain, Jr., *J. Heterocycl. Chem.*, **14**, 1059 (1977).
(2) R. Oesterlin, M. R. Bell, R. H. McGarry, and A. G. Hlavac, *J. Med. Chem.*, **20**, 1068 (1977).
(3) M. R. Bell, A. W. Zalay, R. Oesterlin, S. D. Clemans, D. J. Dumas, J. C. Bradford, and J. Rozitis, Jr., *J. Med. Chem.*, **20**, 537 (1977).
(4) A. C. Shabica, E. E. Howe, J. B. Ziegler, and M. Tishler, *J. Am. Chem. Soc.*, **68**, 1156 (1946).

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