Estrogen Synthetase Inhibitors. 2.[1] Comparison of the in Vitro Aromatase Inhibitory Activity for a Variety of Nitrogen Heterocycles Substituted with Diarylmethane or Diarylmethanol Groups

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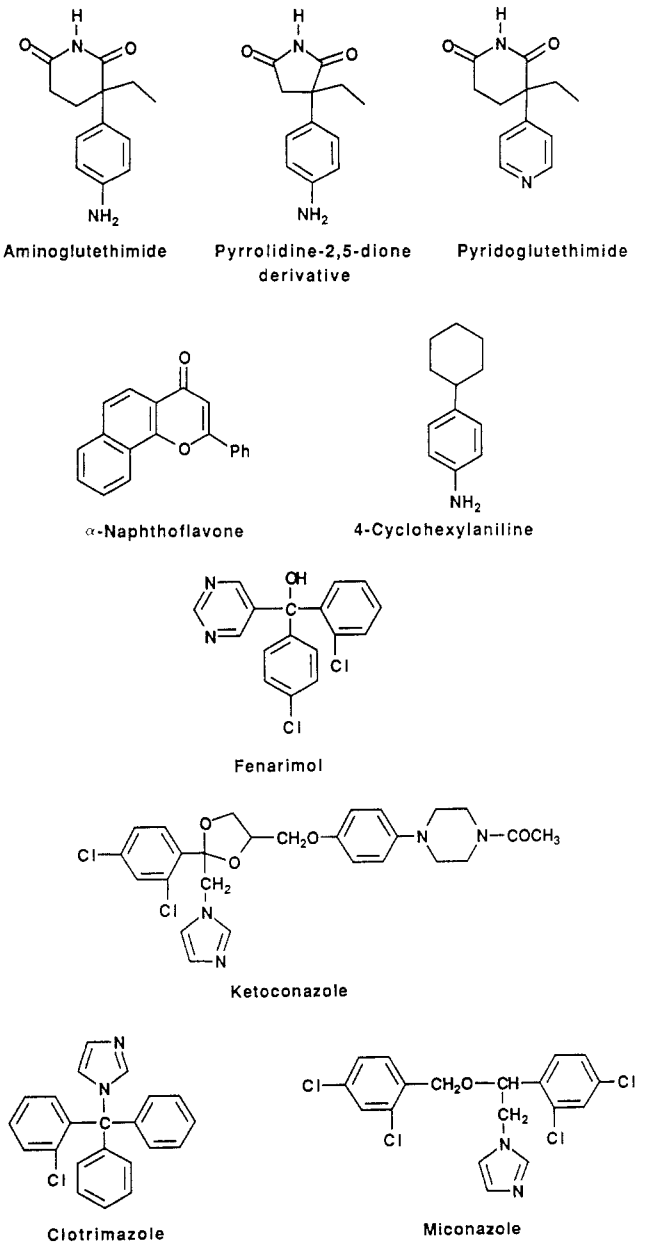
The preparation and in vitro aromatase inhibitory activity of a wide variety of heterocyclic (4,4'-dichlorodiphenyl)methanes and -methanols are described. The choice of the two diaryl-bearing moieties as a vehicle for the evaluation of the heterocycles was made by the comparison of series of imidazole and pyridine-derived compounds with similar pyrimidine compounds reported previously. A structural model for the most active compounds is also presented. The activity of a related series of compounds which contain two heterocyclic moieties was found to be consistent with the model. Many of the compounds evaluated, including representatives of the pyridine, imidazole, pyrimidine, pyrazole, triazole, thiazole, and isothiazole classes, exhibit EC_{50} potencies for aromatase inhibition at low nanomolar levels. These compounds are at least as potent as other nonsteroidal aromatase inhibitors reported previously.

The terminal step in the biosynthesis of estrogens, enzymatic aromatization of androgens, provides an attractive target for selective and effective pharmacological control of estrogen-dependent diseases. Aminoglutethimide (AG, Chart I), which was originally developed as an anticonvulsant,[2] is currently being used in the treatment of metastatic breast cancer[3a-d] on the basis of its ability to inhibit estrogen biosynthesis. As an inhibitor of aromatase, its detailed mechanism of action is quite different from that of the antiestrogen tamoxifen (T), the recognized standard therapy for the treatment of hormonally receptor positive breast cancer.[4] Tamoxifen is believed to act by competing with estrogen for the estrogen receptor. As a result of this interaction with the estrogen receptor, T exhibits partial agonist activity as well as antagonist activity. In contrast to AG, T is devoid of effects on estrogen biosynthesis.

In a recent clinical trial[3d] involving 60 patients with metastatic breast cancer whose disease had progressed on chemotherapy and/or T, AG produced a 33% response rate with mean response duration of 8 months and also showed a small number of complete responders. Aminoglutethimide caused remission at all metastatic sites except lung, whereas other endocrine therapy has previously been shown to be ineffective in treating visceral disease. Responses were also seen in patients who had previously failed to respond to other treatment modalities. Fifty percent of the patients who had responded initially to tamoxifen subsequently responded to AG following failure on T. In patients who had initially failed to respond to T treatment, 26% exhibited objective responses to AG. Thus, the foregoing results suggest that, in addition to its potential use as primary therapy, there may be a significant utility for AG, and possibly other aromatase inhibitors, in the treatment of patients refractory to or having failed on treatment with tamoxifen.

An extremely vigorous quest for steroidal inhibitors of estrogen biosynthesis has been seen in the recent literature.[5] Concurrently, improved nonsteroidal aromatase inhibitors have also been sought, and over the past 10 years, important advancements have been made. For example, the selectivity of AG for aromatase versus sterol-side-chain cleavage has been improved through separation of its enantiomers and finding that the *d* enantiomer is responsible for approximately 90% of the inhibition of aromatase activity of the racemic *d,l* mixture.[6] Several novel aromatase inhibitors (Chart I) which are structurally

Chart I. Some Nonsteroidal Aromatase Inhibitors



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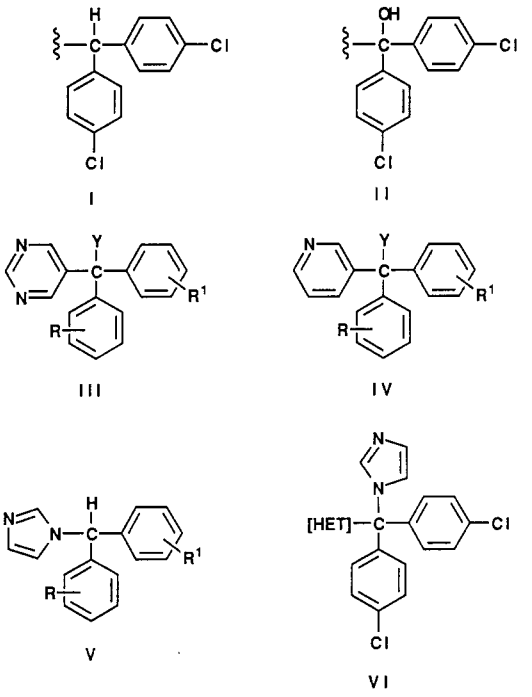
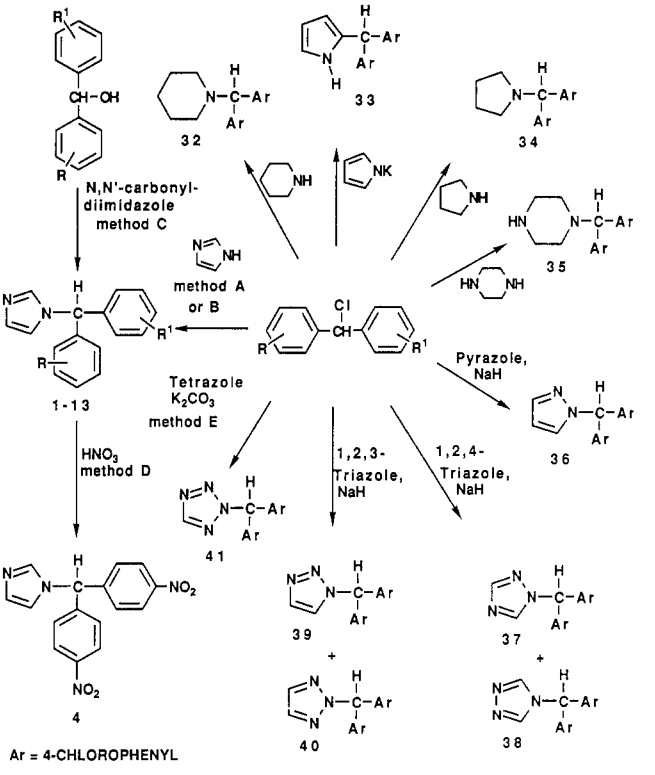
related to AG have also been reported, including 4-cyclohexylaniline,[7] 3-(4′-aminophenyl)pyrrolidine-2,5-dione derivatives,[8] and 3-ethyl-3-(4-pyridyl)piperidine-2,6-dione (pyridoglutethimide).[9] Other less closely related structures, such as α-naphthoflavone,[10] have also been reported to provide novel aromatase inhibitors.

Chart II. Generalized Structures of This Study



Scheme I



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(2) Hoffman, K.; Urech, K. U.S. Patent 2848455, 1958.
(3) (a) For a review of the clinical use of aminoglutethimide both alone and in combination with other antitumor agents including tamoxifen, see: *Cancer Res. Suppl.* **1982**, *42*, 3389s–3467s. (b) Harris, A. L. *Exp. Cell Biol.* **1985**, *53*, 1–8. (c) Sutherland, C. M.; Muchmore, J. H.; Carter, R. D. *South. Med. J.* **1985**, *78*, 987–989. (d) Brufman, G.; Biran, S. *Eur. J. Surg. Oncol.* **1985**, *11*, 27–31. (e) Santen, R. J.; Worgul, W. J.; Samojlik, E.; Interrante, A.; Boucher, A. E.; Lipton, A.; Harvey, H. A.; White, D. S.; Smart, E.; Cox, C.; Wells, S. S. *N. Engl. J. Med.* **1981**, *305*, 545. (f) Santen, R. J.; Brodie, A. H. M. *Clinics in Oncology*; Furr, B. J. A., Ed.; Saunders: London, England, 1982; Vol. 1, 77.
(4) For reviews of the clinical application of tamoxifen to metastatic breast cancer, see: (a) Mouridsen, H.; Palshof, T.; Patterson, J.; Battersby, L. *Cancer Treat. Rev.* **1978**, *5*, 131. (b) Heel, R. C.; Brogden, R. N.; Speight, T. M.; Avery, G. S. *Drugs* **1978**, *16*, 1. (c) Furr, B. J.; Patterson, J. S.; Richardson, D. N.; Slater, S. R.; Wakeling, A. E. In *Pharmacological and Biochemical Properties of Drug Substances*; Goldberg, M. E., Ed.; American Pharmaceutical Association: Washington, D.C., 1979; Vol. 2, pp 335–399.
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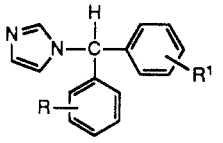
(6) Graves, P. E.; Salhanick, H. A. *Endocrinology* **1979**, *105*, 52–57.
(7) Kellis, J. T., Jr.; Vickery, L. E. *Endocrinology* **1984**, *114*, 2128–2137.
(8) Jones, G. W.; Nazareth, W. M. A.; Daly, M. J.; James, M. I.; Nicholls, P. J.; Smith, H. J. *Anticancer Res* **1986**, *6*, 393.
(9) Foster, A. B.; Jarman, M.; Leung, C.-S.; Rowlands, M. G.; Taylor, G. N.; Plevey, R. G.; Sampson, P. *J. Med. Chem.* **1985**, *28*, 200–204.
(10) Kellis, J. T.; Vickery, L. E. *Science* **1984**, *225*, 1032.

Table I. Diarylsubstituted Imidazolemethanes



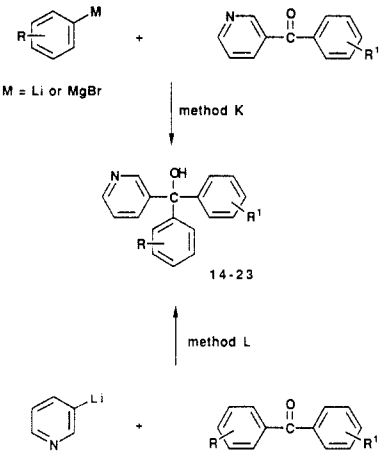
no.	R	R^1	salt or free base (FB)	method of synthesis	mp (bp), °C	% yield	recryst solvent[a]	formula	anal.[b]	in vitro aromatase inhibn: EC_{50},[c] μM
1	H	H	FB	B	87–88	59	EtOAc–ISO	$C_{16}H_{14}N_2$	C,H,N	0.125
2	2-Cl	2-Cl	FB	A	100–113	30	ether–HEX	$C_{16}H_{12}Cl_2N_2$	C,H,N	0.076
3	4-Cl	4-Cl	FB	B	oil	69		$C_{16}H_{12}Cl_2N_2$	C,H,N	0.042
4	$4\text{-}NO_2$	$4\text{-}NO_2$	FB	D	glass	99		$C_{16}H_{12}N_4O_4$	C,H,N	0.040
5	4-F	4-F	FB	A	oil	58		$C_{16}H_{12}F_2N_2$	C,H,N	0.040
6	$2\text{-}OCH_3$	H	HNO_3	B	168–170	20	EtOH	$C_{17}H_{17}N_3O_4$	C,H,N	0.066
7	4-Cl	H	HNO_3	B	129–131	13	EtOH–IPE	$C_{16}H_{14}ClN_3O_3$	C,H,N	0.020
8	$4\text{-}OCH_3$	$4\text{-}OCH_3$	FB	B	oil	20		$C_{18}H_{18}N_2O_2$	C,H,N	0.0125
9	$4\text{-}OCH_3$	$4\text{-}CH_3$	FB	C	oil	7		$C_{18}H_{18}N_2O$	C,H,N	0.0105
10	4-Cl	$4\text{-}CF_3$	FB	C	oil	17		$C_{17}H_{12}ClF_3N_2$	C,H,N	0.0108
11	4-Cl	$4\text{-}OCH_3$	FB	B	oil	75		$C_{17}H_{15}ClN_2O$	C,H,N	0.0084
12	$4\text{-}CH_3$	$4\text{-}CH_3$	FB	B	oil	42		$C_{18}H_{18}N_2$	C,H,N	0.0064
13	4-Br	4-Br	FB	A	oil	9		$C_{16}H_{12}Br_2N_2$	C,H,N	0.0089

[a] ISO, isooctane; DIPE, diisopropyl ether; HEX, hexane; CHEX, cyclohexane; SKB, Skellysolve B. [b] Compounds were analyzed for the elements indicated and were within ±0.4% of the theoretical value except as noted. [c] Concentration required to decrease aromatization of androstenedione in the in vitro rat ovarian microsone assay by 50%.

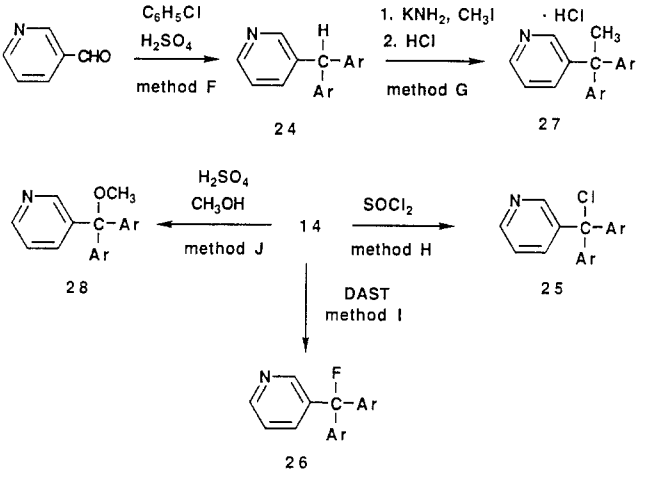
We[1] and others[11] have recently reported the aromatase-inhibiting activities of certain nitrogen heterocyclic compounds related structurally to antifungal agents such as fenarimol, miconazole, ketoconazole, and clotrimazole (Chart I). Such compounds owe their antifungal properties to the inhibition of cytochrome-P450 enzymes. For example, the 14-demethylase is critical to the biosynthesis of ergosterol in the sterol biosynthesis pathway.[12] Inasmuch as the enzymatic conversion of androgens to estrogens is also mediated by cytochrome-P450-based processes,[13] it is understandable that the activity against estrogen synthetase is also observed.

It was hypothesized that the aromatase-inhibition properties would not be restricted to the heterocyclic types represented by the pyrimidine (fenarimol) and imidazole based (miconazole, ketoconazole, and clotrimazole) antifungals but would instead extend to other heterocyclic types, most likely pyridines and triazole derivatives (structures which are well known to be associated with antifungal activities) and probably to other kinds of heterocycles as well. This paper discloses that aromatase-inhibiting properties are, in fact, found in a wide variety of heterocyclic classes. The report details the synthesis and SAR work for the compounds based on a comparison of heterocycles with diarylmethane (I, Chart II) and diarylmethanol moieties (II) as the nonheterocyclic portion of the molecule. The choice of these diaryl one-carbon moieties was based on a comparison of the activities of a series of pyrimidine compounds (III) which was recently described[1] to those of similarly substituted pyridine (IV) and imidazole (V) derivatives. The aromatase inhibition of a related series of C,N-bisheterocyclic derivatives (VI) provides support for the structural model which is proposed for the most active compounds.

Scheme II



Scheme III



Chemistry

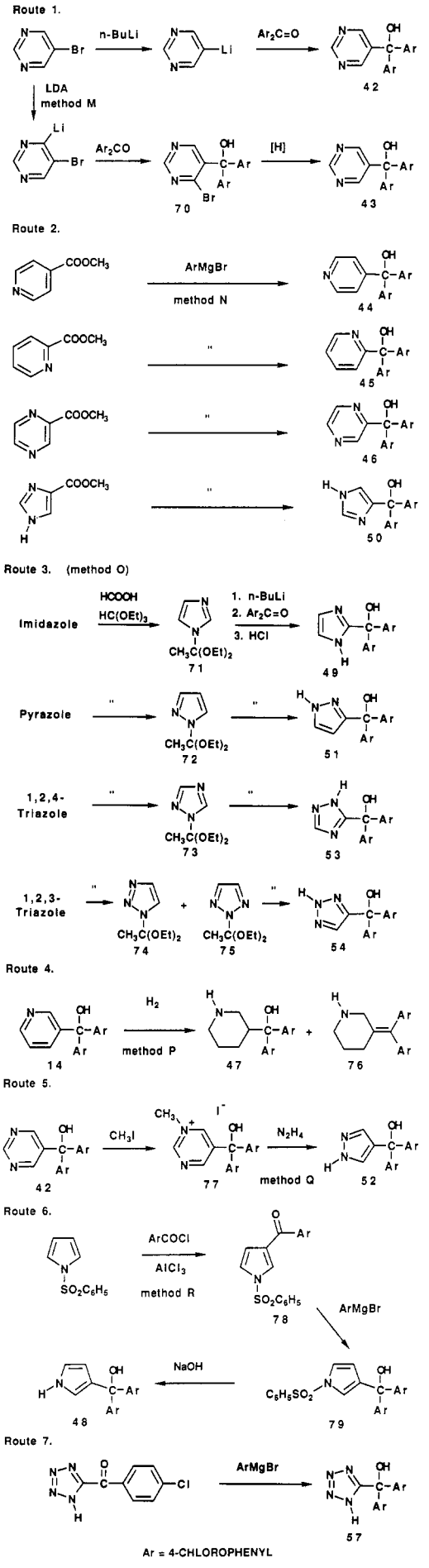
Synthesis of the desired heterocyclic-substituted diarylmethanes, diarylmethanols, and C,N-bisheterocycles

(11) Mason, J. I.; Murry, B. A.; Olcott, M.; Sheets, J. J. *Biochem. Pharmacol.* **1985**, *34*(7), 1087–1092.

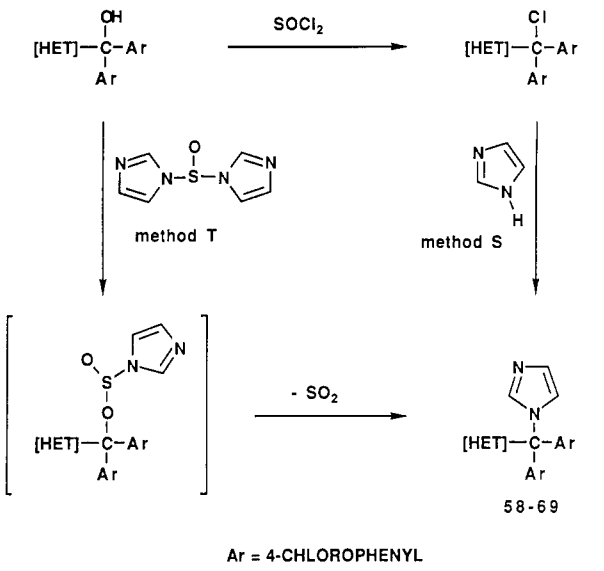
(12) (a) Gadher, P.; Mercer, E. I.; Baldwin, B. C.; Wiggins, T. E. *Pestic. Biochem. Physiol.* **1983**, *19*, 1–10. (b) Bossche, H. V.; Willemsens, G.; Cools, W.; Lauwers, W. F. J.; LeJune, L. *Chem. Biol. Interact.* **1978**, *21*, 59.

(13) Johnston, J. O.; Metcalf, B. W. In *Novel Approaches to Cancer Chemotherapy*; Sunkara, P. S., Ed.; Academic Press, Inc.: Orlando, FL, 1984; p 309. Siiteri, P. K. *Cancer Res. Suppl.* **1982**, *42*, 3269–3273. Thompson, E. A., Jr.; Siiteri, P. K. *J. Biol. Chem.* **1974**, *249*, 5373.

Scheme IV



Scheme V

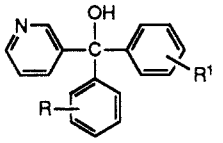


was accomplished by routes shown in Schemes I–V. Most of the imidazole derivatives (Scheme I and Table I) were prepared directly by displacement of Cl from the appropriate benzhydryl chlorides. Two sets of conditions were used to accomplish this transformation: generation of the sodio anion of imidazole by NaH in anhydrous DMF, followed by reaction with the appropriate benzhydryl chloride (method A) or by simply refluxing the benzhydryl chloride with a 3 molar excess of imidazole in anhydrous acetonitrile (method B). In a few instances (compounds **9** and **10**), the direct reaction of the appropriate benzhydrol with carbonyldiimidazole (method C) was used to prepare the imidazolyl products. In a single instance, nitration of compound **1** (method D) was used to prepare 4,4′-dinitro analogue **4**.

Certain other heterocyclic diarylmethanes were also prepared by methods similar to those described above. As shown in Scheme I, compounds **36–40** in Table IV were prepared by generation of the anions of pyrazole, 1,2,4-triazole, or 1,2,3-triazole with NaH followed by reaction with 4,4′-dichlorobenzhydryl chloride. With each of the latter two heterocycles, mixtures of the two possible isomeric N-substituted products were obtained. These isomers were easily separated by chromatography, and their structures were assigned primarily on the basis of their NMR spectroscopy. The 2-substituted pyrrole derivative **33** was obtained similarly, although KH was used in lieu of NaH to prepare the pyrrole potassium salt prior to its reaction with 4,4′-dichlorobenzhydryl chloride. In this way, a low yield of **33** was obtained as the only C-substituted product which was isolated in a pure state. Compounds **32**, **34**, and **35** were readily obtained by the application of method B to piperidine, pyrrolidine, and piperazine, respectively. Reaction of tetrazole with the 4,4′-dichlorobenzhydryl chloride in the presence of K_2CO_3 (method E) provided a low yield of **41**, the structure of which (Figure 1) was determined by X-ray crystallographic analysis.

The preparation of diaryl-3-pyridinylcarbinols (Table II) is depicted in Scheme II. In the majority of cases (compounds **14**, **15**, and **18–22**), a preformed solution of the appropriate aryllithium or aryl Grignard reagent was added to the appropriately substituted 3-aroylpyridine (method K). Alternatively, 3-bromopyridine was transmetalated by *n*-butyllithium to form 3-lithiopyridine, which was then added to an appropriate benzophenone derivative (method L). In this way, compounds **16**, **17**, and

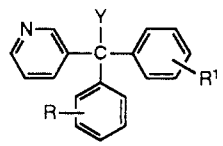
Table II. Diaryl-3-pyridinylcarbinols



no.	R	R^1	salt or free base (FB)	method of synthesis	mp (bp), °C	% yield	recryst solvent[a]	formula	anal.[b]	in vitro aromatase inhibn: EC_{50},[c] μM
14	4-Cl	4-Cl	FB	K	172–174	15		$C_{18}H_{13}Cl_2NO$	C,H,N	0.15
15	4-Cl	H	FB	K	148	61	benzene-SKB	$C_{18}H_{14}ClNO$	C,H,N	>2.0
16	2,4-diCl	H	FB	L	71	18	neat	$C_{18}H_{13}Cl_2NO$	C,H,N	>2.0
17	4-Cl, 2-OCH_3	H	FB	K	115–117	25	Et_2O	$C_{19}H_{16}ClNO_2$	C,H,N	1.8
18	4-Cl	2-Cl	HCl	K	178–186	6	Et_2O	$C_{18}H_{14}Cl_3NO$	C,H,N	>2.0
19	4-Cl	3-CF_3	HCl	K	130–131	25	EtOH–Et_2O	$C_{19}H_{14}Cl_2F_3NO$	C,N[d]	0.65
20	4-Cl	4-CH_3	HCl	K	198–200	20	EtOH–Et_2O	$C_{19}H_{17}Cl_2NO$	C,H,N	0.23
21	4-OCH_3	4-OCH_3	FB	K	145	4	benzene–SKB	$C_{20}H_{19}NO_3$	C,H,N	>2.0
22	3-Cl	3-Cl	FB	K	132–134	59	benzene–SKB	$C_{18}H_{13}Cl_2NO$	C,H,N	4.5
23	2,4-di-Cl	4-F	HCl	L	181	29	acetone–SKB	$C_{18}H_{13}Cl_3FNO$	C,H,N	0.315

[a] ISO, isooctane; DIPE, diisopropyl ether; HEX, hexane; CHEX, cyclohexane; SKB, Skellysolve B. [b] Compounds were analyzed for the elements indicated and were within ±0.4% of the theoretical value except as noted. [c] Concentration required to decrease aromatization of androstenedione in the in vitro rat ovarian microsome assay by 50%. [d] H: calcd, 3.53; found 4.06.

Table III. Diaryl-3-pyridinemethanes



no.	R	R^1	Y	salt or free base (FB)	method of synthesis	mp (bp), °C	% yield	recryst solvent[a]	formula	anal.[b]	in vitro aromatase inhibn: EC_{50},[c] μM
24	4-Cl	4-Cl	H	FB	F	(204–208/5 mm)	22		$C_{18}H_{13}Cl_2N$	C,H,N	0.084
25	4-Cl	4-Cl	Cl	HCl	H	116–117	100	benzene–SKB	$C_{18}H_{13}Cl_4N$	C,H,N	0.20
26	4-Cl	4-Cl	F	FB	I	oil	44	–	$C_{18}H_{12}Cl_2FN$	C,H,N	0.20
27	4-Cl	4-Cl	CH_3	HCl	G	175–177	70	EtOAc	$C_{19}H_{16}Cl_3N$	C,H,N	0.145
28	4-Cl	4-Cl	OCH_3	HCl	J	amorph	52	–	$C_{19}H_{16}Cl_3NO$	C,H,N	1.60

[a] ISO, isooctane; DIPE, diisopropyl ether; HEX, hexane; CHEX, cyclohexane; SKB, Skellysolve B. [b] Compounds were analyzed for the elements indicated and were within ±0.4% of the theoretical value except as noted. [c] Concentration required to decrease aromatization of androstenedione in the in vitro rat ovarian microsome assay by 50%. [d] No analysis was attempted.

23 were prepared. The thiazolyl- and isothiazolylcarbinols (Table V) were also prepared by method L via transmetalation of 5-bromothiazole[14] and direct lithiation of unsubstituted isothiazole,[15] respectively.

Diaryl-3-pyridinylmethanes (Table III) were prepared as depicted in Scheme III. The parent compound **24** was prepared by condensing pyridine-3-carboxaldehyde with chlorobenzene in concentrated H_2SO_4 (method F). Alkylation of **24** ($KNH_2/NH_3/CH_3I$) provided the corresponding methylated compound, which was isolated as hydrochloride salt **27**. Other compounds (**25**, **26**, and **28** in Table III) were obtained from carbinol **14**. Accordingly, reaction of **14** with thionyl chloride (method H) provided **25**; fluorination with DAST, (diethylamido)sulfur trifluoride (method I), gave **26** and ionization in acidic media in the presence of methanol (method J) led to the methoxy compound **28**, all in moderate to excellent yield.

The heterosubstituted (dichlorodiphenyl)methanes in Table IV in which the heterocyclic moiety is attached through a carbon atom were prepared as follows: Compounds **30** and **31** were prepared by method F described above by using pyridine-4-carboxaldehyde or pyridine-2-carboxaldehyde, respectively, in lieu of 3-pyridinecarboxaldehyde. Pyrimidine analogue **29** was prepared by the reduction of compound **42** as described previously.[1]

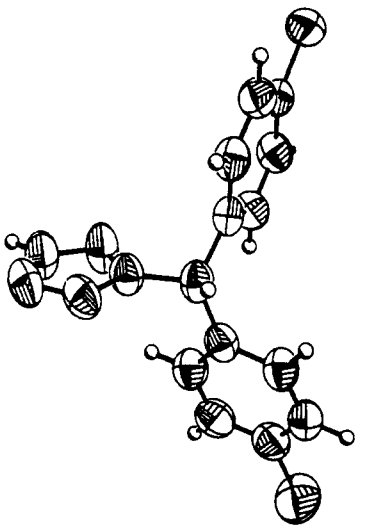
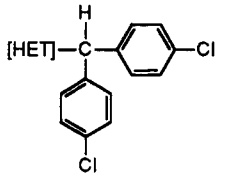


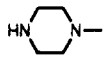
Figure 1. X-ray crystallographic structure of 2-[bis(4-chlorophenyl)methyl]-2*H*-tetrazole (**41**).

The heterosubstituted (4,4′-dichlorodiphenyl)methanols (Table V) were obtained by a variety of synthetic routes as depicted in Scheme IV. As described previously,[1] direct transmetalation of 5-bromopyrimidine to provide 5-

(14) Beyerman, H. C.; Berbebn, P. H.; Bontekoe, J. S. *Recl. Trav. Chim. Pays-Bas* **1954**, *73*, 325–332.
(15) Caton, M. P. L.; Jones, D. H.; Slack, R.; Wooldridge, K. H. R. *J. Chem. Soc.* **1964**, 446.

Table IV. Heterosubstituted (Dichlorodiphenyl)methanes



no.	HET	salt or free base (FB)	method of synthesis	mp (bp), °C	% yield	recryst solvent[a]	formula	anal.[b]	in vitro aromatase inhibn: EC_{50},[c] μM
29		FB	–	oil	87	–	$C_{17}H_{12}Cl_2N_2$	C,H,N	0.055
30		FB	F	(218/0.3 mm)	24	–	$C_{18}H_{14}Cl_3N$	C,H[e]	0.160[d]
31		FB	F	200–224	28	–	$C_{18}H_{13}Cl_2N$	C,H,N	>5.0
32		FB	B	78–79	66	MeOH	$C_{18}H_{19}Cl_2N$	C,H,N	>5.0
33		FB	A	oil	9	–	$C_{17}H_{13}Cl_2N$	C,H,N	>5.0
34		HCl	β	130–135	7	Et_2O	$C_{17}H_{18}Cl_3N$	C,H,N	>5.0
35		FB	B	107–108	60	HEX	$C_{17}H_{18}Cl_2N_2$	C,H,N	1.93
36		FB	A	oil	89		$C_{16}H_{12}Cl_2N_2$	C,H,N	>2.0
37		FB	A	112–114	86	EtOAc–ISO	$C_{15}H_{11}Cl_2N_3$	C,H,N	0.0088
38		FB	A	148–151	12	Et_2O	$C_{15}H_{11}Cl_2N_3$	C,H,N	0.0093
39		FB	A	124–125	55	toluene	$C_{15}H_{11}Cl_2N_3$	C,H,N	0.0185
40		FB	A	oil	43		$C_{15}H_{11}Cl_2N_3$	C,H,N	>5.0
41		FB	E	91–92	8	MeOH	$C_{14}H_{10}Cl_2N_4$	C,H,N	0.150

[a] ISO, isooctane; DIPE, diisopropyl ether; HEX, hexane; CHEX, cyclohexane. [b] Compounds were analyzed for the elements indicated and were within ±0.4% of the theoretical value except as noted. [c] Concentration required to decrease aromatization of androstenedione in the in vitro rat ovarian microsome assay by 50%. [d] Compound tested as the HCl salt. [e] N: calcd, 4.46; found, 4.91.

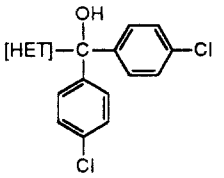
lithiopyrimidine and reaction with 4,4′-dichlorobenzophenone provided **42**. Alternatively, lithiation of 5-bromopyrimidine by the method of Kress[16] and addition to 4,4′-dichlorobenzophenone at −78 °C to produce **70** followed by catalytic removal of the 5-bromo group (method M) provided the 4-substituted pyrimidine derivative **43** (route 1). Compounds **44–46** and **50** were prepared by general method N. This method consisted of the addition of the appropriate methyl ester (methyl imidazole-4-carboxylate,[17] methyl isonicotinate, methyl picolinate, or 2-carbomethoxypyrazine[18]) to an excess of (4-chlorophenyl)magnesium bromide in THF as shown (route 2).

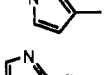
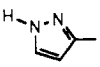
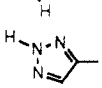
In only certain cases described above (compounds **42**, **43**, **14**, **55**, and **56**) were the parent metalated, i.e. Grignard or organolithium, heterocycles readily available for synthesis of the (4,4′-dichlorodiphenyl)methanols. In many instances, the presence of acidic N–H protons on the parent heterocycle made the requisite metalated heterocycles inaccessible. Therefore, the authors turned to the lithiation of suitably protected heterocycles as a solution to this problem. Toward that end, 1,1-diethoxyethyl (DEE) protective groups were employed (method O) as shown in route 3. Previous workers have used the similar, homologous dimethoxymethyl protective moiety for purposes similar to those described here.[19] By the DEE protective group method, the 2-imidazolyl- (**49**), 3-pyrazolyl- (**51**), 5-(1,2,4)-triazolyl- (**53**), and 5-(1,2,3)-triazolylcarbinols (**54**) shown in Table V were prepared from the corresponding DEE-protected heterocycles (**71–75**).

Several of the other carbinols in Table V were prepared by methods specific for their synthesis: The reduced piperidinylcarbinol **47** was isolated in rather low yield following catalytic reduction of the corresponding pyridinylcarbinol **14** (method P, route 4). Also isolated as a byproduct of this reduction was olefinic piperidine derivative **76**. 4-Pyrazolylcarbinol **52** was synthesized by conversion of the pyrimidine moiety of compound **42** to the

(16) Kress, T. J. *J. Org. Chem.* **1979**, *44*, 2081.
(17) Pyman, F. L. *J. Chem. Soc.* **1916**, *109*, 186.
(18) Sugimoto, N.; Tanaka, T. *J. Pharm. Soc. Jpn.* **1956**, *76*, 470–471.
(19) Curtis, N. J.; Brown, R. S. *J. Org. Chem.* **1980**, *45*, 4038–4040.

Table V. Heterosubstituted (Dichlorodiphenyl)methanols



no.	HET	salt or free base (FB)	method of synthesis	mp (bp), °C	% yield	recryst solvent[a]	formula	anal.[b]	in vitro aromatase inhibn: EC_{50},[c] μM
42		FB	L	159–161	55	toluene–HEX	$C_{17}H_{12}Cl_2N_2O$	C,H,N	0.071
43		FB	M	150–152	64	MeOH	$C_{17}H_{12}Cl_2N_2O$	C,H,N	0.322
44		FB	N	204–206.5	11	EtOH	$C_{18}H_{13}Cl_2NO$	C,H,N[e]	0.084[d]
45		FB	N	685–700	46	ISO	$C_{18}H_{13}Cl_2NO$	C,H,N	>5.0
46		FB	N	116–117	5	SKB	$C_{17}H_{12}Cl_2N_2O$	C,H,N	0.094
47		FB	P	199–201	25	Et_2O	$C_{18}H_{19}Cl_2NO$	C,H,N	>5.0
48		FB	R	oil	33		$C_{17}H_{13}Cl_2NO$	*f*	ND[g]
49		FB	O	196–197	60	EtOAc–HEX	$C_{16}H_{12}Cl_2N_2O$	C,H,N	0.670
50		FB	N	110–113	50	Ether–HEX	$C_{16}H_{12}Cl_2N_2O$	C,H,N	0.028
51		FB	O	136–138	76	Et_2O–toluene	$C_{16}H_{12}Cl_2N_2O$	C,H,N	0.09
52		FB	Q	135–137	58	$CHCl_3$–Et_2O	$C_{16}H_{12}Cl_2N_2O$	C,H,N	0.03
53		FB	O	233–234	72	MeOH–H_2O	$C_{15}H_{11}Cl_2N_3O$	C,H,N	>2.0
54		FB	O	203–204	17	EtOAc–HEX	$C_{15}H_{11}Cl_2N_3O$	C,H,N	2.00
55		FB	L	148–150	29	Et_2O	$C_{16}H_{11}Cl_2NOS$	C,H,N	0.0096
56		FB	L	118–119.5	66	CHEX	$C_{16}H_{11}Cl_2NOS$	C,H,N	0.019
57		FB	K	210–210.5	86	EtOAc–HEX	$C_{14}H_{10}Cl_2N_4O$	C,H,N	>5.0

[a] ISO, isooctane; DIPE, diisopropyl ether; HEX, hexane; CHEX, cyclohexane; SKB, Skellysolve B. [b] Compounds were analyzed for the elements indicated and were within ±0.4% of the theoretical value except as noted. [c] Concentration required to decrease aromatization of androstenedione in the in vitro rat ovarian microsome assay by 50%. [d] Compound tested as the HCl salt. [e] N: calcd, 4.24; found, 3.67. [f] *M*/e calcd 317.0374, found 317.0360. [g] ND, not determined due to the instability of **48**.

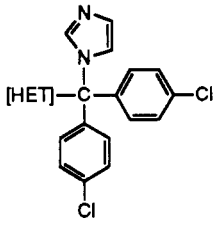
desired pyrazole function. This transformation, which has been described previously,[20] is based on the ring contraction of *N*-methylpyrimidinium salts into pyrazoles on treatment with hydrazine (method Q). For the specific case of compound **42**, crude methiodide salt **77** was used without extensive purification, and an acceptable yield of the desired **52** was obtained without difficulty as shown in route 5.

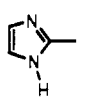
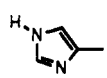
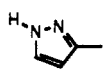
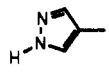
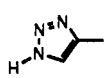
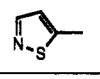
An attempt was made to prepare 3-pyrrolylcarbinol **48** in pure form. Compound **48** was synthesized (route 6; method R) by application of a route described by Kakushima[21] for the synthesis of 3-acylpyrroles to provide **78**.

(20) Brouwer, M. S.; van der Plas, H. C.; van Veldhuizen, A. *Recl. Trav. Chim. Pays-Bas*, **1978**, *97*, 110–112.

(21) Kakushima, M.; Hamel, P.; Frenette, R.; Rokach, J. *J. Org. Chem.* **1983**, *48*, 3214–3219.

Table VI. Dichlorodiphenyl Bisheterocycles



no.	HET	method of synthesis	mp (bp), °C	% yield	recryst solvent[a]	formula	anal.[b]	in vitro aromatase inhibn: EC_{50},[c] μM
58		T	165–167	53	EtOAc–ISO	$C_{20}H_{14}Cl_2N_4$	C,H,N	0.026
59		S	122–124	19	benzene-SKB	$C_{21}H_{15}Cl_2N_3$	C,H,N	0.050
60		S	144–146	72	Et_2O	$C_{21}H_{15}Cl_2N_3$	C,H,N	0.050
61		T	133–133.5	49	EtOAc–ISO	$C_{21}H_{15}Cl_2N_3$	C,H,N	0.0285
62		T	190–195	34	Et_2O	$C_{19}H_{14}Cl_2N_4$	C,H,N	0.0094
63		T	170–173	30	EtOAC–ISO	$C_{19}H_{14}Cl_2N_4$	C,H,N	0.016
64		T	214–216	38	MeOH	$C_{19}H_{14}Cl_2N_4$	C,H,N	0.061
65		T	157–160	22	Et_2O–HEX	$C_{19}H_{14}Cl_2N_4$	C,H,N	0.0110
66		T	188–191	44	MeOH	$C_{18}H_{13}Cl_2N_5$	C,H,N	0.0113
67		T	155–156	25	HEX	$C_{18}H_{13}Cl_2N_5$	C,H,N	0.018
68		T	138–140	68	CH_2Cl_2–HEX	$C_{19}H_{13}Cl_2N_3S$	C,H,N	0.017
69		T	148–150	47	EtOAc–CHEX	$C_{19}H_{13}Cl_2N_3S$	C,H,N	0.057

[a] ISO, isooctane; DIPE, diisopropyl ether; HEX, hexane; CHEX, cyclohexane; SKB, Skellysolve B. [b] Compounds were analyzed for the elements indicated and were within ±0.4% of the theoretical value except as noted. [c] Concentration required to decrease aromatization of androstenedione in the in vitro rat ovarian microsome assay by 50%.

Addition of an excess of (4-chlorophenyl)magnesium bromide to **78** followed by removal of the sulfonyl protective group with strong base provided **48** as an oil. The compound was obtained as essentially a single entity as determined by NMR spectroscopy, and its identity was demonstrated by high-resolution mass measurement. An exact elemental analysis was not obtained, due to the instability of compound **48** and attendant difficulties in removing traces of solvents from the oily product without simultaneously causing its decomposition. 5-Substituted tetrazole **57** (route 7) was prepared in a manner which utilized the approach of method K. Thus, addition of 5-(4-chlorobenzoyl)tetrazole[22] to an excess of (4-chlorophenyl)magnesium bromide in THF provided directly compound **57** in a yield of 86%.

Lastly, a series of compounds containing two heterocyclic moieties was prepared from the corresponding carbinol compounds listed in Table V. The C,N-bisheterocycles (Table VI) were synthesized by the two methods shown in Scheme V. For carbinols which formed reasonably stable chlorides, reaction with $SOCl_2$, followed by displacement with imidazole (method S), provided **59** and **60**. A superior method[23] for the synthesis of such compounds was the direct reaction of the carbinols with sulfinyldiimidazole, which was readily generated from imidazole and $SOCl_2$ in acetonitrile (method T). This latter method was applied to all of the other compounds (**58**, **61–69**) in Table VI.

Biological Results and Discussion

An assay was established to identify active inhibitors of aromatase for further evaluation in in vivo systems. Inhibition of aromatase activity was determined by using a modification of the rat ovarian microsome assay described by Brodie[24] et al. In this assay, ovarian microsomes from

(22) Fisher, B. E.; Tomson, A. J.; Horwitz, J. P. *J. Org. Chem.* **1959**, *24*, 1650.

(23) Draber, W.; Regel, E. U.S. Patent 3,897,438, July 29, 1975.

rats treated with pregnant mares serum gonadotropin were incubated with [^{3}H]androstenedione and an NADPH-generating system. Aromatization of the substrate resulted in the release of [^{3}H]water, which was quantified by liquid-scintillation spectrometry. From an initial SAR study of 5-substituted pyrimidine derivatives,[1] we hypothesized that in vitro aromatase-inhibition properties would most likely be found in compounds in which a heterocyclic moiety is attached to a (4,4′-dichlorodiphenyl)methane or -methanol moiety. Furthermore, the earlier finding that **29** and **42** had nearly equal potency suggested that information from both the methane- and methanol-derived series could be assembled to provide a better overall understanding of the role of the heterocyclic groups which were to be investigated. This combination of data was especially useful in these cases where, by virtue of attachment of the aryl-bearing moiety to a nitrogen atom of the heterocycle, the methanol-derived structures were unstable, thereby limiting comparisons to the methane-derived series. Thus, two hypotheses were constructed.

1. The 4,4′-dichlorodiphenyl substitution would be highly active in heterocyclic series other than pyrimidines.
2. The (4,4′-dichlorodiphenyl)methane- and (4,4′-dichlorodiphenyl)methanol-derived moieties would provide analogues of about the same degree of potency in other heterocyclic series.

To test these hypotheses, two series deemed most likely to include active aromatase inhibitors, the 1-imidazolylmethanes and 3-pyridylmethanols, were examined.

Aryl Moiety Modifications in 1-Imidazolylmethanes

Aromatase inhibition in vitro was determined for the series of imidazole derivatives shown in Table I. Of the 13 compounds examined, every one was a highly potent (EC_{50} < 0.2 μM) inhibitor of the microsomal aromatase enzyme. In retrospect, this was not particularly surprising because 1-alkyl- or 1-aryl-substituted imidazoles have been reported to be excellent inhibitors of other cytochrome P-450 enzymes.[25-27] For the purpose of this study, however, the strong inhibitory effects of these derivatives (**1–13**) at the levels tested obscured the smaller changes in activity expected from variation of the aromatic substituents. Thus, under the assay conditions used, for heterocycles (such as imidazole) which interact extremely strongly with the heme Fe of cytochrome P-450, alterations in structure in the nonheterocyclic portion of the molecule did not produce major changes in inhibitory activity. Under more stringent kinetic analysis than that used in the present study, however, differences might be found that could be attributed to the nonheterocyclic moiety.

Aryl Moiety Modifications of 3-Pyridinemethanols

The investigation of the 3-substituted pyridinylcarbinol series (Table II) was more enlightening even though the compounds as a group were less active than the imidazoles just described. As expected from earlier work with pyrimidines,[1] greatest inhibitory activity was found in the compounds (**14, 19, 20, 23**) which were substituted with electron-withdrawing substituents, particularly two chloro groups. Maximal activity was achieved when the two chloro moieties were at the 4- and 4′-positions, exactly as predicted. Replacing one chloro by hydrogen (**15**) or moving one chloro to the 2-position (**18**) or both chloro groups to the 3- and 3′-positions (**22**) resulted in diminished activity. Fluorine was found to enhance activity over H (**16, 23**). Other substituents (**17, 19**) maintained activity, but to a lesser degree. Overall, the results nicely parallel those determined earlier for the variation of aryl substituents in the pyrimidinylcarbinol series,[1] although the pyridinylcarbinols are generally, as a class, less active. Having thus validated hypothesis no. 1, further studies with 4,4′-dichlorodiphenyl substitution were carried out.

Y Modifications of (4,4′-Dichlorodiphenyl)methanes

To test the second hypothesis that the methane and methanol moieties would have about the same activity, compound **14** (Table II) was compared with **24** and the other compounds in Table III. In a consistent fashion, the changes in the Y substituent mirrored those found earlier for pyrimidine derivatives:[1] when the Y groups were small, for example H, OH, Cl, F, and CH_3 (**24, 14, 25, 26, 27**), there was little change in the activity as all were highly potent inhibitors. However, larger groups, such as methoxy, considerably reduced the activity (**28**). Most importantly, however, the activity of carbinol **14** was only slightly less than that of **24**, the corresponding methane, thus lending credence to hypothesis no. 2. Both compounds were the most active members in their respective series. Therefore, it was concluded that, for the purposes of further study (investigation of a variety of heterocyclic types and their influence on aromatase inhibition), it was reasonable to proceed with the (dichlorodiphenyl)methane and -methanol derivatives which have been employed for compounds **29–69** of this study.

Heterocyclic Modifications

Since both the methane derivatives (Table IV) and the methanols (Table V) gave similar conclusions, they are discussed together. Of nearly equal importance to the choice of heterocycle was the way in which it was attached to the dichlorodiphenyl-bearing moiety. One compound (**29**) from the earlier pyrimidine series has been shown to interact strongly with rat ovarian microsomal cytochrome P-450.[28] The compound induced a reverse type I binding spectrum at all concentrations tested (6–266 μM), which is indicative of interaction with the Fe of cytochrome P-450 and the nitrogen of the pyrimidine moiety. It was hypothesized that attachment of the dichlorodiphenyl-bearing moiety at a position on or near N might preclude the interaction with Fe and thereby destroy aromatase-inhibition activity. This relationship was borne out in every case examined. Attachment of the organic moiety to the nitrogen of the heterocycle directly (**32, 34, 35**) or to a position adjoining (α to) nitrogen (**31, 33, 40, 45, 49**) led to loss of aromatase-inhibiting properties *unless* an additional N was present and situated in the heterocycle at a more remote locus (**37, 38, 39, 43, 46, 50, 51**). If the additional nitrogen was not correctly positioned, inactivity resulted (**36, 40**). For optimal activity, attachment of the dichlorodiphenyl-bearing moiety must be one position removed (β) from the nitrogen (**14, 29, 42, 52, 55, 56**) although some activity arose through γ attachment (**30, 44**). Note, however, the β attachment was a necessary, but not sufficient, condition for inhibitory activity: the cases **41**,

(24) Brodie, A. H. M.; et al. *Endocrinology* **1977**, *100*, 1684–1695.
(25) Wilkinson, C. F.; Hetnarski, K.; Cantwell, G. P.; DiCarlo, F. J. *Biochem. Pharmacol.* **1974**, *23*, 2377.
(26) Rogerson, T. D.; Wilkinson, C. F.; Hetnarski, K. *Biochem. Pharmacol.* **1977**, *26*, 1039.
(27) Wilkinson, C. F.; Hetnarski, K.; Denison, M. S.; Guengerich, F. P. *Biochem. Pharmacol.* **1983**, *32*, 997.
(28) Lindstrom, T. D.; Whitaker, G. W. *Fundam. Appl. Toxicol.* **1987**, *8*, 595–604.

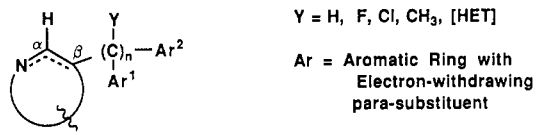


Figure 2. Postulated features for the most highly active aromatase inhibitors (see the text for further discussion).

47, **53**, **54**, and **57** exhibited the β-attachment characteristic, but they were inactive as aromatase inhibitors.

The reduction state of the heterocycles was also considered with regard to aromatase-inhibitory properties. Although **32**, **34**, and **35** were not expected to be active on the basis of their structural arrangements as described above, **47** provided a direct comparison to the unreduced pyridine **14**. Clearly, reduction to the more basic and more polar piperidine leads to essential loss of the enzyme inhibition of activity. One possible explanation for this result is that it is the sp^2 rather than sp^3 hybridized N orbital which most effectively interacts with Fe in the aromatase P-450 enzyme. Alternatively, the reduced (piperidine) analogue might be excessively polar and/or basic to interact efficiently with the aromatase-active site. From the foregoing results, combined with our earlier work,[1] a structural model was formulated for the most active aromatase inhibitors in the series (Figure 2).

Studies were also extended to a series of structures which contain more than one heterocyclic ring (i.e. bisheterocycles, Table VI). Certain compounds of this general class are known to be effective antifungal agents.[23] Therefore, compounds **58–69** were examined as potential aromatase inhibitors. The model (Figure 2) predicts that the introduction of a 1-imidazoyl group as the second heterocyclic moiety, as conducted in Scheme V, would lead to an active inhibitor in every case, since the 1-substituted imidazole has an sp^2 nitrogen β to the position of attachment to the (dichlorodiphenyl)methyl group. (In this interpretation of the model, the heterocycle originally present becomes the Y group.) In fact, *all* of the compounds **58–69** in Table VI were found to be highly active aromatase inhibitors. Even those examples which were derived from a monoheterocyclic carbinol with little (**45**) or no (**49**, **53**, **54**) aromatase inhibition were highly active following introduction of the second heterocycle. In view of the ability of the imidazole derivatives to interact strongly with P-450 enzymes as stated earlier, further studies are needed to fully define the relationships between the structure and mode of attachment of the second heterocycle and the resulting aromatase-inhibitory activity. In summary, a wide variety of heterocyclic types have been evaluated for their aromatase-inhibiting properties through the use of their (4,4′-dichlorophenyl)methane or -methanol derivatives. A structural model has been developed and it is serving to guide further studies, for example those of bisheterocyclic derivatives. Many of the compounds are at least as, if not more, potent than the other nonsteroidal aromatase inhibitors previously reported.[1,10,11] Some of the best compounds are active at low nanomolar levels and, as such, have sufficient potency to merit further investigation in vivo. One must consider, however, that these compounds may be interacting with other P-450 enzymes besides aromatase. Thus, effects may be seen on impairment of drug metabolism or other P-450-mediated processes which may severely limit their use. If these or related compounds can be found which inhibit aromatase without compromising the other P-450 systems, they may well provide clinical candidates with significant advantages over aminoglutethimide.

Experimental Section

Methods. Melting points were determined with a Thomas-Hoover capillary melting point apparatus and are uncorrected. Infrared spectra were recorded on a Nicolet 10MX Fourier transform spectrometer and ultraviolet spectra were taken on a Cary 219 instrument. Proton NMR spectra were determined at 60 MHz on a Varian T-60 NMR spectrometer, at 90 MHz on a JEOL FX-90Q spectrometer, at 100 MHz on a Varian HA-100 instrument, at 270 MHz on a Bruker WM270 machine, or at 300 MHz on a General Electric QE-300 spectrometer using tetramethylsilane as internal standard. Mass spectra were obtained on a Finnegan MAT731 spectrometer in the EI mode with samples introduced directly into the ion source or in the FD mode using carbon dendrite emitters for the spectral determination. X-ray analysis was conducted with a Nicolet P2 four-angle diffractometer using monochromatic copper radiation. Although only selective spectral data are presented herein, all new compounds exhibited IR, UV, and NMR spectra consistent with the structures assigned to them. Microanalyses were performed at Eli Lilly and Co., and results are within 0.4% of the calculated values except as noted. Most of the starting materials are commercially available or well-known in the literature. Preparative HPLC work was carried out using a Waters Prep 500A machine with one normal-phase silica gel cartridge unless specified otherwise. Yields have not been maximized and in many cases were much higher than the amounts of pure products which were eventually obtained as indicated in the tables.

Synthesis of Heterocyclic Diarylmethanes. Method A. Synthesis of 1-[Bis(4-chlorophenyl)methyl]-1*H*-1,2,4-triazole (37) and 4-[Bis(4-chlorophenyl)methyl]-4*H*-1,2,4-triazole (38). To anhydrous DMF (150 mL) at 25 °C under a N_2 atmosphere was added NaH (2.88 g, 0.12 mol) as a suspension (60%) in mineral oil. The mixture was gently heated on the steam bath and 1,2,3-triazole (10.0 g, 0.145 mL) was added gradually in small portions. When the vigorous evolution of H_2 had ceased, the mixture was heated on the steam bath for 15 min and cooled to 25 °C, and (4,4′-dichlorodiphenyl)chloromethane (10.0 g, 0.037 mol) was added. The reaction mixture was heated on the steam bath for 4 h. Most of the DMF was removed under reduced pressure, and the residue was dissolved in H_2O (200 mL) and EtOAc (200 mL). The EtOAc layer was separated, washed with brine, dried over $MgSO_4$, filtered, and evaporated to provide the crude product mixture of **37** and **38**, which were separated by chromatography using 2:1 toluene–EtOAc as eluent. Appropriate fractions gave 9.6 g (86%) of colorless, oily **37**, which subsequently crystallized from EtOAc–isooctane. Anal. ($C_{15}H_{11}Cl_2N_3$) C, H, N, Cl. This material, which melted at 112–114 °C, was confirmed by NMR spectroscopy to be the expected major 2-substituted triazole product. Further elution fractions of the column by a step gradient to 9:1 EtOAc–MeOH provided fractions which contained 1.4 g (12%) of a colorless oil, which crystallized from ether. By NMR spectral determination, this material, mp 148–150 °C, was 4-substituted triazole isomer **38**. Anal. ($C_{15}H_{11}Cl_2N_3$) C, H, N, Cl. Also prepared by this same general method were **2**, **5**, **13**, **36**, **39**, and **40**. Compound **33** was also prepared similarly except that KH was used in lieu of NaH.

Method B. Synthesis of 1-(Diphenylmethyl)imidazole (1). In a 1-L flask fitted with a magnetic stirrer and condenser and charged with a nitrogen atmosphere were combined imidazole (20.4 g, 0.30 mol), CH_3CN (200 mL), and chlorodiphenylmethane (benzhydryl chloride, 20.3 g, 0.10 mol). After heating of the reaction on the steam bath at reflux for 2 h, TLC (silica gel, toluene) showed the reaction to be essentially complete. The mixture was evaporated to near dryness, 300 mL of EtOAc and 300 mL of aqueous $NaHCO_3$ solution were added, and the EtOAc layer was separated. The organic phase was washed repeatedly with brine, dried over anhydrous K_2CO_3, filtered, and evaporated to a nearly colorless oil. The material was purified by chromatography using a gradient of 1:1 toluene–EtOAc (2 L) to 9:1 EtOAc–MeOH (2 L) as the eluting solvent.

Appropriate fractions yielded 14.8 g of a single material as a colorless oil, which crystallized. Further purification by recrys-

tallization from EtOAc–isooctane gave 13.8 g (58.9%) of the desired 1, mp 87–88 °C. Anal. ($C_{16}H_{14}N_2$) C, H, N. Additional diaryl-substituted imidazolemethanes also prepared by the above method from imidazole and the appropriate benzhydryl chlorides were **3**, **6**, **7**, **8**, and **12**. Similarly prepared from 4,4′-dichlorobenzhydryl chloride and the corresponding cyclic amines were **32** (from piperidine), **34** (from pyrrolidine), and **35** (from piperazine). In the case of the pyrrolidine analogue **34**, the hydrochloride salt was prepared by dissolving the free base in ether and adding excess gaseous HCl in ether to precipitate the product, which soon afterward crystallized on standing.

Method C. Synthesis of 1-[(4-Methoxyphenyl)(4-methylphenyl)methyl]-1*H*-imidazole (9). A mixture of 4-methyl-4′-methoxybenzhydrol (11.0 g, 0.048 mol) and carbonyldiimidazole (12.0 g, 0.074 mol) in dichloroethane (200 mL) was refluxed for 3 days under a nitrogen atmosphere. The reaction mixture was cooled, decanted from the solids present, and washed with water. The solvents were removed in vacuo, and the residue was chromatographed over silica gel using ethyl acetate. A slow moving spot which ran on TLC (silica gel, EtOAc) with an R_f of approximately 0.2 was isolated and determined to be **9** (1.0 g, 7%) as an oil. Anal. ($C_{18}H_{18}N_2O$) C, H, N. In a similar manner, compound **10** was prepared from carbonyldiimidazole and the corresponding benzhydrol.

Method D. Synthesis of 1-[Bis(4-nitrophenyl)methyl]-imidazole (4). *N*-(Diphenylmethyl)imidazole (**1**, 6.00 g, 0.025 mol) was dissolved in 25 mL of concentrated sulfuric acid. To this solution was added dropwise 70% nitric acid (5.00 g, 0.055 mol) diluted with an equal volume of concentrated sulfuric acid. During the addition, the temperature of the reaction mixture was kept at approximately 35 °C with an ice bath. After all the nitric acid had been added, the flask was slowly heated to 60 °C and maintained at that temperature for 1 h. The solution was cooled and poured onto 500 g of ice, which precipitated a heavy oil. After basification at room temperature with excess $NaHCO_3$, the oil was extracted with EtOAc (2 × 100 mL); the organic layer was washed with water (3 × 25 mL), separated, and dried over anhydrous $MgSO_4$. The solvent was removed to provide an oily material, which was purified by chromatography over silica gel with elution initially by EtOAc–toluene (1:1), followed by EtOAc, and finally EtOAC–EtOH (9:1). Concentration of the appropriate fractions provided 8.2 g (99%) of **4**, which did not crystallize but gave satisfactory analytical data. Anal. ($C_{16}H_{12}N_4O_4$) C, H, N.

Method E. Synthesis of 2-[Bis(4-chlorophenyl)-methyl]-2*H*-tetrazole (41). In a 1-L, one-neck round-bottom flask fitted with magnetic stirrer, condenser, and N_2 inlet and heated in an oil bath were combined 1*H*-tetrazole (3.12 g, 0.045 mol), DMF (150 mL), anhydrous K_2CO_3 (26.8 g, 0.190 mol), and (4,4′-dichlorodiphenyl)chloromethane (10.0 g, 0.037 mol). The reaction was heated for 2.5 h at 85–90 °C and then held overnight at 60–65 °C. The reaction mixture was then poured into 1 L of brine and extracted with 2 × 200 mL of EtOAc. The EtOAc layer was washed with 3 × 25-mL portions of aqueous brine, dried ($MgSO_4$), and evaporated to provide **41**, as a pale yellow oil. The crude product was purified by chromatography eluting with toluene. Fractions were collected of 230 mL each. Fractions 8 and 9 contained the desired product as 1.1 g (8%) of a yellow oil. Crystals, mp 91–92 °C, were obtained from methanol. Anal. ($C_{14}H_{10}Cl_2N_4O$) C, H, N. After determining that the product had the expected M^+ peak (m/e 305), a sample of **41** was submitted for NMR experiments to determine whether it had the structure of a 1-substituted or 2-substituted tetrazole. Since no NOE was found between the benzhydryl CH and the proton on the tetrazole ring, the structure of a 2-substituted tetrazole was favored. Subsequently, an X-ray structure determination for crystals obtained by slow evaporation of a toluene solution confirmed the 2-substituted tetrazole structure for **41**.

Method F. Synthesis of Bis(4-chlorophenyl)-3-pyridylmethane (24). Chlorobenzene (150 g, 1.33 mol) and H_2SO_4 (200 g, 2.0 mol) were cooled to 0 °C and combined, and pyridine-3-carboxaldehyde (25 g, 0.23 mol) was added with stirring. The mixture was allowed to warm to room temperature overnight. Then it was poured into ice and washed with Et_2O, and the ether-insoluble oil plus the aqueous phase was neutralized with sodium bicarbonate. The crude product was then extracted with Et_2O, dried over $MgSO_4$, filtered, and distilled to yield 20 g (22%) of **24**, bp 204–8 °C (0.5 Torr). Anal. ($C_{18}H_{13}Cl_2N$) C, H, N. Compounds **30** and **31** were prepared in similar reactions starting with 4-pyridinecarboxaldehyde and 2-pyridinecarboxaldehyde, respectively.

Method G. Synthesis of 3-[α-Methyl-α-bis(4-chlorophenyl)methyl]pyridine Hydrochloride (27). To freshly prepared potassium amide [from addition of potassium metal (0.39 g, 0.01 mol) to ammonia] in approximately 10 mL of liquid ammonia was added **24** (3.14 g, 0.01 mol). The ammonia was replaced with dry Et_2O (10 mL), and the reaction was allowed to cool to room temperature. A large excess of methyl iodide (1.0 mL) also dissolved in dry ether (2.5 mL) was then added. The mixture was stirred for 45 min and then washed with water. The ether layer was separated, dried over anhydrous $MgSO_4$, and evaporated to dryness to provide 3.1 g of a colorless oil. The NMR spectrum of the crude product showed approximately 70% of the desired methylated product and 30% unreacted **24**. The mixture was separated by chromatography on a Waters Prep 500A instrument with a single RPC18 reverse-phase cartridge. Elution with 60:40 CH_3CN–0.5% $(NH_4)H_2PO_4$ buffer gave a satisfactory separation, but several runs, none exceeding 2 g, were required to obtain a clean separation of the mixture. The appropriate fractions were pooled and the CH_3CN was removed on a rotary evaporator. The free base of **27** was subsequently extracted from the residual aqueous solution by 2 × 200 mL of EtOAc. After drying of the EtOAc extracts over $MgSO_4$, filtration, and evaporation, the desired free base was obtained as a colorless oil (1.75 g, 54%). A 1.5-g sample of the oil was converted to the hydrochloride salt by gaseous HCl in $CHCl_3$. Evaporation of the solvent and recrystallization of the residue provided 1.66 g (99%) of **27** as white crystals, which melted at 175–177 °C. Anal. ($C_{19}H_{15}Cl_2N$·HCl) C, H, N.

Method H. Synthesis of α-Chloro-α-3-pyridyl-α-(4,4′-dichlorodiphenyl)methane Hydrochloride (25). 3-Pyridylcarbinol **14** (4.2 g, 0.127 mol) in a 1-L round-bottom flask under a N_2 atmosphere was treated with thionyl chloride (10 mL). The solid rapidly dissolved upon slight warming of the reaction mixture on a steam bath. After the last of the solid had dissolved, the reaction mixture was allowed to stand for 30 min. The resulting yellow solution was concentrated under vacuum. The amorphous white residual foam was treated with dry benzene (100 mL) and concentrated to provide a quantitative yield of a slightly hygroscopic solid, which exhibited satisfactory spectral properties. Recrystallization from benzene–Skellysolve B gave white crystals, mp 116–117 °C, but elemental analysis for the crystals was not as good as that of the amorphous product initially obtained. Anal. ($C_{18}H_{12}Cl_3N$·HCl) C, H, N.

Method I. Synthesis of 3-[Bis(4-chlorophenyl)fluoromethyl]pyridine (26). To a solution of carbinol **14** (5.0 g, 0.015 mol) in 40 mL of methylene chloride under a N_2 atmosphere was added (diethylamido)sulfur trifluoride (DAST, 2.4 g, 0.015 mol). The reaction was allowed to stir at 25 °C for 16 h. The solution was then washed with water (100 mL) and with saturated aqueous sodium bicarbonate solution until basic. The organic phase was separated, dried over anhydrous $MgSO_4$, filtered, and evaporated. Crude **26** was purified by chromatography over silica gel using EtOAc–hexane (1:5). Concentration of the appropriate fractions provided 2.2 g (44%) of oily material, which was one spot on TLC and gave satisfactory spectral and elemental data. Anal. ($C_{18}H_{12}Cl_2FN$) C, H, N.

Method J. Synthesis of α,α-Bis(4-chlorophenyl)-α-3-pyridylmethyl Methyl Ether Hydrochloride (28). Carbinol **14** (5.0 g, 0.015 mol) was dissolved in 25 g of concentrated H_2SO_4. The resulting reddish-brown solution was transferred to an addition funnel and added dropwise to 60 mL of cold methanol. During the addition, the temperature was held at 0 °C or lower by means of a salt–ice bath. As soon as all of the acidic solution had been added, the resulting mixture was poured into a mixture of excess sodium hydroxide and ice. The product was extracted with Et_2O, and the organic layer was separated, washed with water, and dried over $MgSO_4$. After evaporation to dryness, a very viscous, yellow oil was obtained. Efforts to induce the oil to crystallize were unsuccessful; therefore, it was dissolved in dry Et_2O and converted to **28** by addition of dry HCl. The hydrochloride (3.0 g) was amorphous, and efforts to crystallize it were also unsuccessful. However, **28** provided spectral data and an

elemental analysis consistent with theory. Anal. ($C_{19}H_{15}Cl_2NO$·HCl) H, N; C: calcd, 59.93; found, 59.52.

Synthesis of Heterocyclic Diarylmethanes. Method K. Synthesis of α,α-Bis(*p*-chlorophenyl)-3-pyridinemethanol (14). Magnesium (2.4 g, 0.10 g-atom) was reacted with 4-bromochlorobenzene (23 g, 0.12 mol) with iodine as catalyst and Et_2O as solvent. After all the Mg was consumed, the Grignard reagent was transferred under a N_2 atmosphere to a dropping funnel and added dropwise to a stirred solution of 4-chlorophenyl 3-pyridyl ketone (10.8 g, 0.05 mol) in Et_2O (200 mL) at 0 °C. The resulting suspension was stirred overnight while it was allowed to warm to room temperature. Excess saturated aqueous NH_4Cl solution was added to the reaction mixture. The ether layer was separated and subsequently extracted several times with dilute HCl solution. The aqueous extract was charcoaled, cooled, and made alkaline with 1 N NaOH. The basic aqueous mixture was extracted with Et_2O several times and the Et_2O layer was separated, dried over anhydrous $MgSO_4$, filtered, and evaporated in vacuo. The residue was recrystallized from benzene–Skellysolve B to provide 2.5 g (15%) of **14**, mp 172–174 °C. Anal. ($C_{18}H_{13}Cl_2NO$) C, H, N. Compounds **15**, **18**, **20**, and **21** were prepared in a similar manner from the appropriately substituted Grignard reagents and 3-aroylpyridines. In similar addition reactions, compounds **19** and **22** were prepared by the addition of the aryllithium reagents (prepared from 3-bromobenzotrifluoride and 3-chlorobromobenzene, respectively) to the appropriate chlorinated benzoylpyridines. Compound **57** was prepared similarly from (4-chlorophenyl)magnesium bromide and 5-carbomethoxy-1*H*-tetrazole.

Method L. Synthesis of α-(2,4-Dichlorophenyl)-α-(4-fluorophenyl)-3-pyridinemethanol Hydrochloride (23). To 3-bromopyridine (16 g, 0.1 mol) in 300 mL of anhydrous Et_2O under a nitrogen atmosphere was added dropwise at −60 to −70 °C *n*-butyllithium (0.1 mol). After the addition was complete, the reaction was kept cold and was stirred for 5 h. Then, 2,4-dichloro-4′-fluorobenzophenone was added dropwise in 100 mL of Et_2O while the temperature was maintained below −60 °C. Following an additional 5 h of stirring, the reaction was allowed to reach room temperature with stirring overnight. The reaction mixture was decomposed with 200 mL of concentrated ammonium chloride solution, the organic layers were separated, and the aqueous layer was again extracted with fresh Et_2O. The combined Et_2O extracts were dried over potassium carbonate and concentrated to provide a residue, which crystallized from acetone–Skellysolve B to provide 11 g (29%) of the free base of **23**, mp 105 °C. Two grams of the free base were converted to the hydrochloride salt by treatment with dry HCl in Et_2O to provide an analytical sample, mp 181 °C. Anal. ($C_{18}H_{12}Cl_2FNO$·HCl) C, H, N. The addition of 3-pyridyllithium to 2,4-dichlorobenzophenone and 4-chloro-2-methoxybenzophenone provided **16** and **17**, respectively, by this same general method. Thiazole derivative **55** was obtained similarly from 5-bromothiazole, *n*-butyllithium, and 4,4′-dichlorobenzophenone. Direct lithiation of isothiazole at the 5-position in THF at −78 °C by 1.05 equiv of *n*-BuLi followed by addition of 4,4′-dichlorobenzophenone gave compound **56**.

Method M. Part I. Synthesis of α,α-Bis(4-chlorophenyl)-5-bromo-4-pyrimidinemethanol (70). A solution of lithium diisopropylamide (LDA) was prepared as follows: to diisopropylamine (8.06 g, 0.08 mol) in anhydrous THF (50 mL) under N_2 at −30 °C was added rapidly by syringe 1.5 M *n*-BuLi in hexane (53.3 mL, 0.08 mol). After stirring of the mixture at −30 °C for 5 min, it was transferred to a dropping funnel, which was surrounded with a jacket containing dry ice. The LDA solution was then added dropwise under N_2 to a solution of 5-bromopyrimidine (12.7 g, 0.08 mol) and 4,4′-dichlorobenzophenone (20 g, 0.08 mol) in THF (50 mL) at 26 °C. The dark yellow solution which resulted was stirred for 16 h and then poured into ice (500 g), H_2O (500 mL), and EtOAc (500 mL). The EtOAc layer was separated, washed with brine (3 × 100 mL), dried over $MgSO_4$, filtered, and evaporated to provide a yellow oil (32 g), which was purified by chromatography using the Waters Prep 500A instrument and two normal-phase silica gel cartridges. Elution with a gradient system of toluene (2 L) to 4:1 toluene–EtOAc (2 L) served to separate the desired **70**. Appropriate fractions were concentrated to give **70** in a yield of 12.6 g (38%), mp 132–133 °C (EtOAc–isooctane). Anal. ($C_{17}H_{11}BrCl_2N_2O$) C, H, N.

Method M. Part II. Synthesis of α,α-Bis(4-chlorophenyl)-4-pyrimidinemethanol (43). Compound **70** (3.0 g, 0.0073 mol) was hydrogenated over Raney nickel (5 g) in a mixture of EtOAc (90 mL) and triethylamine (1.5 g) at 25 °C and an initial H_2 pressure of 60 psi for 12 h. After filtration of the reaction mixture, a pale yellow solution was obtained. The solution was washed with water (50 mL), 1 N HCl (2 × 50 mL), and brine (2 × 50 mL). After the solution had been dried over anhydrous $MgSO_4$, it was filtered and evaporated to a light yellow oil. The oil soon crystallized, and recrystallization from MeOH gave the desired product **43** as small, white needles, mp 150–152 °C, in a yield of 1.54 g (64%). Anal. ($C_{17}H_{12}Cl_2N_2O$) C, H, N.

Method N. Preparation of α,α-Bis(4-chlorophenyl)-1*H*-imidazole-5-methanol (50). Magnesium (4.7 g, 0.19 g-atom) was placed in a 1-L, flame-dried flask under a nitrogen atmosphere. Four drops of 1,2-dibromoethane in 2 mL of Et_2O were added followed by the gradual addition of 4-bromochlorobenzene (25.0 g, 0.13 mol) in 100 mL of THF. When all of the aryl bromide had been added, the reaction was stirred at ambient temperature until the reaction subsided and then for 2 h longer. The resulting Grignard reagent was then treated with methyl imidazole-4-carboxylate (5.0 g, 0.04 mol) in 50 mL of THF at a rapid dropwise rate of addition, and the resulting reaction mixture was refluxed for 1 h. Evaporation of most of the THF, followed by decomposition of the reaction mixture over excess iced ammonium chloride solution, extraction of the product with 3 × 100 mL of EtOAc, drying of the extracts over $MgSO_4$, filtration, and evaporation, provided the product as a pale yellow oil, which weighed 11 g. The crude material was purified with silica chromatography and gradient elution consisting of 3 L of EtOAc gradually changing to 3 L of 15% MeOH in EtOAc (v/v). Appropriate fractions provided a colorless oil, which gave white crystals from Et_2O–hexane, 6.47 g (50%). Spectral analysis was satisfactory, but the elemental analysis was slightly off; therefore, a 1-g sample was recrystallized from benzene to provide 540 mg of the desired **50**, mp 110-113 °C. Anal. ($C_{16}H_{12}Cl_2N_2O$) C, H, N. Also prepared by this same general method were compounds **44** (from methyl isonicotinate), **45** (from methyl picolinate), and **46** (from 2-carbomethoxypyrazine).

Method O. Part I. Synthesis of 1-(1,1-Diethoxyethyl)-imidazole (71). Imidazole (54.4 g, 0.8 mol) was dissolved in triethyl orthoacetate (324 g, 368 mL, 2.0 mol) under a nitrogen atmosphere, and 1 mL of 98% formic acid was added. The combined ingredients were heated overnight in a 125 °C oil bath, so as to distill the generated EtOH from the reaction mixture. The following day, the temperature of the bath was gradually increased until much of the remaining excess triethyl orthoacetate was distilled out. The resulting liquid was an approximate equal mixture of **71** and triethyl orthoacetate by NMR spectroscopy. After the addition of 2 g of anhydrous Na_2CO_3 to the liquid, it was distilled under vacuum. At first, the remaining orthoacetate was collected and then, as the temperature was raised, **71** (bp 97–103 °C/6 mm) was obtained as a colorless liquid in a yield of 117.2 g (80%). This material was used in subsequent transformations without further purification. Additional diethoxyethyl derivatives were similarly prepared from triethyl orthoacetate, formic acid, and the parent heterocycle as follows. (a) 1-(1,1-Diethoxyethyl)pyrazole (**72**) (bp 72–76 °C/8 mm) was obtained in a yield of 71% when the preparation was run on a 0.4-mol scale. (b) 1-(1,1-Diethoxyethyl)-1,2,4-triazole (**73**) was obtained in a yield of 48% and had bp 94–97 °C (9 mm). Following distillation, there was no evidence by NMR spectroscopy for the presence of the isomeric 4-(1,1-diethoxyethyl)-1,2,4-triazole in the final product. (c) 1-(1,1-Diethoxyethyl)-1,2,3-triazole (**74**) and 2-(1,1-diethoxyethyl)-1,2,3-triazole (**75**) were obtained as an approximately 1:1 mixture following distillation (bp 82–85 °C/10 mm) of the reaction mixture from a 0.07-mol scale reaction. All of the above protected heterocycles were clear, colorless liquids, which could be stored indefinitely over anhydrous Na_2CO_3 at room temperature.

Method O. Part II. Synthesis of α,α-Bis(4-chlorophenyl)-1*H*-imidazole-2-methanol (49). To **71** (9.25 g, 0.05 mol) in anhydrous Et_2O (150 mL) under a nitrogen atmosphere at −40 °C was added *n*-butyllithium as a 1.3 M solution in hexane (38.5 mL, 0.05 mol). This addition produced a white suspension, which

was stirred for 20 min at −40 °C. The 4,4′-dichlorobenzophenone was then added as a solid in a single portion. After stirring of the reaction for 2 h, it was allowed to warm to room temperature. TLC (silica gel, EtOAc–toluene 1:1) showed the loss of ketone and formation of a new, slower moving spot. Ice was added, and the pH was first adjusted to 3 with cold 1 N HCl and then raised to 7 with concentrated ammonia. The resulting amorphous solid was dissolved by addition of EtOAc (400 mL). The organic layer was washed with 3 × 100 mL of aqueous brine, dried over anhydrous K_2CO_3, filtered, and evaporated to a white solid. Recrystallization of the solid from EtOAc–hexane and drying overnight at room temperature in vacuo provided 28.9 g (60%) of the desired **49**, mp 196–197 °C. Anal. ($C_{16}H_{12}Cl_2N_2O$) C, H, N.

Heterocyclic carbinol compounds **51**, **53**, and **54** were also prepared by the above method from the appropriate diethoxyethyl derivatives and 4,4′-dichlorobenzophenone. In every case, adjustment of the pH to approximately 3 during the workup served to completely cleave the N-protective groups and generate the final products.

Method P. Synthesis of α,α-Bis(4-chlorophenyl)-3-piperidinemethanol (47) and 3-[Bis(4-chlorophenyl)-methylene]piperidine (76). Compound **14** (6.0 g, 0.0182 mol) was hydrogenated in 170 mL of ethanol and 20 mL of concentrated HCl for 16 h, with platinum dioxide catalyst (2.0 g) and an initial H_2 pressure of 60 psi. After filtration of the catalyst, the reaction mixture was filtered through Filter-cel, and the filtrate was evaporated to a foam. The foam was dissolved in water, basified to pH 10 with 50% NaOH, and extracted with 3 × 100 mL of EtOAc. The combined EtOAc extracts were washed with water and with brine, dried over anhydrous $MgSO_4$, and evaporated to a white foam. TLC (silica gel, 5% methanol in chloroform) showed much starting material and 2 slower moving spots. Chromatography over silica gel initially eluting with 10% MeOH in chloroform changing with a gradient to 30% MeOH in chloroform over a total of 6 L provided unreduced starting material (1.6 g) followed by the two lower R_f spots. The first of these to elute was 840 mg (15%) of essentially pure **76**, which melted at 108–110 °C following recrystallization from Et_2O–hexane. Anal. ($C_{18}H_{17}Cl_2N$) C, H, N. Further elution of the column provided 1.6 g (27%) of a yellow foam, which was found to be the desired carbinol **47**. Off-white crystals, mp 199–201 °C, were obtained following recrystallization from EtOH–Et_2O. Anal. ($C_{18}H_{19}Cl_2NO$) C, H, N.

Method Q. Synthesis of α,α-Bis(4-chlorophenyl)-1*H*-pyrazole-4-methanol (52). Compound **42** (10 g, 0.03 mol) was refluxed overnight with 100 mL of methyl iodide. The reaction was then cooled and filtered to provide 12.8 (90%) of crude methiodide salt **77**. This material was used as follows without further purification: To a slurry of **77** (12.8 g, 0.027 mol) in 75 mL of absolute EtOH was added a solution of anhydrous hydrazine (3.0 g, 0.093 mol) in 25 mL of absolute EtOH. The mixture was heated to reflux, and initially the solids went into solution, but subsequently a precipitate began to form. Water (25 mL) was added, and the mixture was refluxed for an additional 20 min and then filtered hot. The filtrate was diluted with enough water to make the volume 500 mL. Extraction of the product from the filtrate with 500 mL of Et_2O followed by drying over anhydrous K_2CO_3 and evaporation of the ether provided the desired **52**. Crystals, mp 135–137 °C, were obtained from chloroform containing a few drops of ether in a yield of 8.67 g (58%). Anal. ($C_{16}H_{12}Cl_2N_2O$) C, H, N, Cl.

Method R. Part I. Synthesis of 1-(Phenylsulfonyl)-3-(4-chlorobenzoyl)pyrrole (78). In a 250-mL, three-neck, round-bottom flask fitted with a condenser, magnetic stirrer, and an addition funnel, 4-chlorobenzoyl chloride (9.6 g, 6.9 mL, 0.05 mol) was added slowly under N_2 to aluminum chloride suspended in 100 mL of 1,2-dichloroethane at 25 °C. The resulting red solution was stirred for 10 min, and then a solution of 1-benzenesulfonyl pyrrole (10 g, 0.0482 mol) in 20 mL of 1,2-dichloroethane was added over a 15-min period. The reaction mixture was stirred for 1.5 h at 25 °C and subsequently quenched by pouring it over 400 mL of ice + water. The organic layer was separated, and the aqueous layer was extracted with methylene chloride (2 × 100 mL). The combined organic layers were washed with 3 × 50 mL of H_2O and twice with brine. After drying over magnesium sulfate and evaporation, a thick, viscous oil, which soon crystallized, was obtained. Following recrystallization from 3A ethanol, **78** was obtained as 14.9 g (89%) of small, white needles, mp 95–97 °C. Anal. ($C_{17}H_{12}NO_3S$) C, H, N.

Method R. Part II. Synthesis of α,α-Bis(4-chlorophenyl)-1-(phenylsulfonyl)pyrrole-3-methanol (79). In a 250-mL, three-neck, round-bottom flask fitted with a condenser, magnetic stirrer, and dry-ice acetone bath, *n*-butyllithium (20 mL of 1.5 M solution in hexane) was added dropwise under N_2 to 4-bromochlorobenzene (5.7 g, 0.03 mol) in 50 mL of THF at −78 °C. A white precipitate soon formed. The mixture was stirred for 10 min, then a solution of **78** (10.0 g, 0.029 mol) in 30 mL of THF, was added over a 20-min period. The cold bath was removed, and the yellow solution began to darken. Stirring was continued as the reaction warmed to room temperature. TLC (silica gel, EtOAc–toluene 1:9) showed disappearance of **78** and formation of a slightly slower running spot. Ice water (50 mL) was added slowly to the reaction mixture, and most of the THF was removed on a rotary evaporator. The gum which precipitated was dissolved in EtOAc and the organic layer was separated from the aqueous phase. The aqueous phase was extracted with 2 × 25 mL of EtOAc, and the organic extracts were combined and washed with water (2 × 100 mL) and brine (2 × 100 mL). After drying over anhydrous magnesium sulfate and evaporation to a brown oil, the product was chromatographed with 3% EtOAc in toluene for elution solvent. Combination of the appropriate fractions and concentration gave 10.9 g (82%) of the desired **79**. Although the compound was essentially pure by NMR spectroscopy, the colorless oil failed to crystallize and began to darken and decompose upon standing at room temperature. Therefore, **79** was used without purification for the synthesis of **48**.

Method R. Part III. Synthesis of α,α-Bis(4-chlorophenyl)-1*H*-pyrrole-3-methanol (48). In a 1-L, round-bottom flask fitted with a condenser, magnetic stirrer, and heating mantle, 5 N sodium hydroxide (100 mL) was added under N_2 to compound **79** (9.9 g, 0.022 mol) and dioxane (100 mL) at 25 °C. After the reaction was refluxed overnight, TLC (silica gel, EtOAc–toluene 1:9) showed loss of **79** and appearance of a major spot corresponding to the desired material. The reaction mixture was cooled to room temperature and 200 mL of water was added. Most of the dioxane was evaporated, and the aqueous mixture was extracted with Et_2O (3 × 100 mL). The combined organic extracts were washed with water and brine, dried over anhydrous sodium sulfate, and evaporated to a dark oil, which weighed 6 g. Crude **48** was purified by silica gel chromatography with 3% EtOAc in toluene. Combination and evaporation of the appropriate fractions provided a colorless oil (2.3 g, 33%), which began to darken upon standing at room temperature. By physical chemistry determination, including high-resolution mass spectral determination, the material was essentially a single substance, and the structure was that of the desired **48**. However, an exact elemental analysis was not obtained.

Synthesis of Bisheterocyclic Diarylmethanes. Method S. Synthesis of 3-[Bis(4-chlorophenyl)-1-imidazolylmethyl]pyridine (59). Compound **14** (16.5 g, 0.05 mol) in methylene chloride (75 mL) was treated with thionyl chloride (7.1 g, 0.06 mol) and refluxed for 30 min. Excess thionyl chloride was removed under a vacuum. The residue was dissolved in 100 mL of acetonitrile, and imidazole (6.8 g, 0.1 mol) was added. The mixture was refluxed for 1 h, allowed to cool, poured onto ice, and acidified with 3 N HCl. After adjustment of the pH to approximately 8.5 with 1 N sodium hydroxide, the product was extracted with Et_2O. The Et_2O solution was dried over anhydrous $NaSO_4$, and the solvent was removed under vacuum. The residue was then chromatographed over silica gel using elution with ethyl acetate followed by acetone to fully displace the product. The appropriate fractions were concentrated to provide an oil, which was recrystallized twice from benzene–Skellysolve B to provide the desired compound **59**, mp 122–124 °C, in a yield of 3.6 g (19%). Anal. ($C_{21}H_{15}Cl_2N_3$) C, H, N. Compound **60** was prepared in a similar manner from the corresponding carbinol intermediate **44**.

Method T. Synthesis of 1-[Bis(4-chlorophenyl)-1*H*-imidazol-4-ylmethyl]-1*H*-imidazole (63). Imidazole (1.70 g, 0.025 mol) was dissolved in 20 mL of acetonitrile in a 50-mL Erlenmeyer flask capped with a rubber septum. Rapid injection of thionyl chloride (0.93 g, 0.56 mL, 0.00783 mol) produced an immediate precipitation of imidazole hydrochloride. After stirring

of the mixture for 5 min at room temperature, it was filtered through a glass frit. The resulting filtrate was cooled to near 0 °C and then combined with a solution of compound **50** (2.0 g, 0.0063 mol) in 25 mL of acetonitrile at 0 °C. The reaction was then stirred for 30 min at ice-bath temperature, whereupon TLC (silica gel, EtOAc) showed no remaining starting material and a slower running spot. To the reaction mixture were added EtOAc (50 mL), saturated $NaHCO_3$ solution (25 mL), and ice (50 g). The organic layer was separated, washed with brine and sodium bicarbonate solution, and dried over anhydrous K_2CO_3. Removal of the solvent provided an oily solid, which weighed 1.85 g. White crystals were obtained from EtOAc–isooctane and amounted to 0.69 g (30%) of the desired compound **63**, mp 170–173 °C. Anal. ($C_{19}H_{14}Cl_2N_4$) C, H, N. Compounds **58**, **61–69** were also prepared by method T starting from the appropriate carbinol intermediates.

Aromatase Inhibition in Vitro. Ovarian microsomes were prepared from rats treated with pregnant mares serum gonadotropin (PMSG, Sigma Chemical Co., St. Louis, MO) every other day for 12 days. Sample vials contained the microsomes (protein = 665 μg/vial), a drop of propylene glycol, 0.1 μM androstenedione (Steraloids Inc., Wilson, NH), [1,2-^{3}H]androstenedione (100 000 dpm, 46.1 Ci/mmol, New England Nuclear Corp., Boston, MA), and the test compound (0.005–10.0 μM) dissolved in a total volume of 2.5 mL of 0.1 M phosphate buffer, pH 7.4, containing 0.0012% dithiothreitol. The reaction was initiated by the addition of an NADPH-generating system (0.5 mg of $NADP^+$; 1.0 mg of glucose-6-phosphate; 3 IU glucose-6-phosphate dehydrogenase, Sigma Chemical Company, St. Louis, MO). The K_m for androstenedione in this assay system was determined to be approximately 71.1 nM. After a 10-min incubation at 37 °C in an atmosphere of 95% O_2–5% CO_2, the reaction was stopped by the addition of 10.0 mL of chloroform, and the samples were stored overnight at 4 °C. A 1.0-mL aliquot of the aqueous phase was incubated with 1.0 mL of a 2.5% charcoal suspension [Norit charcoal (neutral), Sigma Chemical Co., St. Louis, MO] in a phosphate buffer for 10 min. The samples were centrifuged at 600*g* for 10 min, and 1.0 mL of the supernatant was added to a vial containing 10 mL of Amersham PCS (Amersham Corp., Arlington Heights, IL). Samples were analyzed by liquid-scintillation spectrometry. In this assay, the aromatization of the labeled androstenedione results in the release of [^{3}H]H_2O. The extent of aromatization was quantified on the basis of the difference between vials incubated in the presence and absence of fenarimol and a correction for the spontaneous release of labeled water. Activity is expressed as concentration of the test compound that inhibits 50% of the enzyme activity (EC_{50}).

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Supplementary Material Available: Tables listing X-ray diffraction study data of 2-[bis(4-chlorophenyl)methyl]-2*H*-tetrazole (**41**) (6 pages). Ordering information is given on any current masthead page.