titration depended on the compound and the temperature (range = 1.8×10^{-3} to 4.0×10^{-4} M DNA-P).

Thermal Melting. Thermal melting studies were carried out in MES 00 buffer at 260 nm with a compound/DNA-P molar ratio of 0.2. A Cary 219 spectrophotometer equipped with a five-sample compartment with an automatic sample changer and a Neslab temperature bath and programmer was used to collect the data.

Acknowledgment. This work was supported by NSF Grant PCM83-09575. W.D.W. is the recipient of an American Cancer Society Faculty Research Award (FRA-267). We thank Robert Jones and Dr. Fred Henneike for assistance in interfacing and programming the Apple II computer–Cary 219 spectrometer.

Registry No. 1, 92078-84-7; 2, 69408-73-7; 3, 92078-85-8; 4, 69408-86-2; 5, 92078-86-9; 3-(dimethylamino)propylamine, 109-55-7; 1,8-naphthalic anhydride, 81-84-5; 3-nitro-1,8-naphthalic anhydride, 3027-38-1; disodium 3-amino-1,8-naphthalenedicarboxylate, 92078-87-0; acenaphthene, 83-32-9; 4-nitroacenaphthene, 1015-74-3; 4-nitro-1,8-naphthalic anhydride, 6642-29-1; 4-amino-1,8-naphthalic anhydride, 6492-86-0.

Bulky Amine Analogues of Ketoprofen: Potent Antiinflammatory Agents

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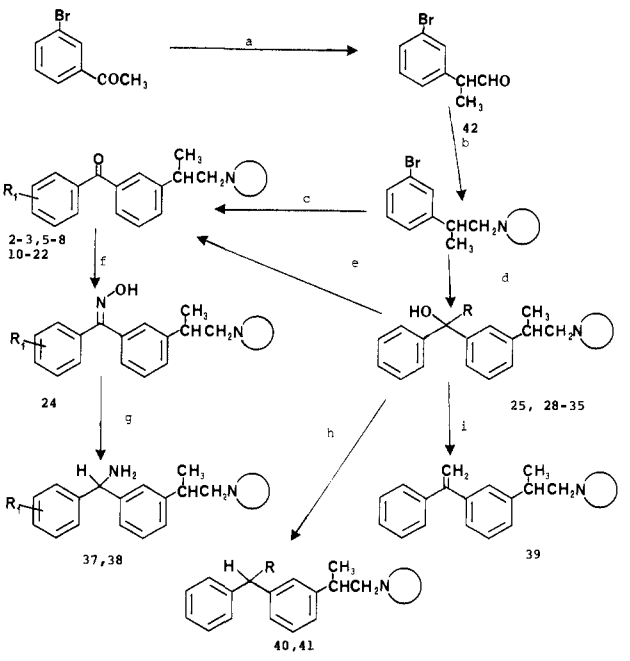
Replacement of the carboxyl group of 2-(3-benzoylphenyl)propionic acid (Ketoprofen) with various bulky amines has produced a series of highly active antiinflammatory agents that have reduced intestinal ulcerogenicity and have better therapeutic ratios in the 21-day adjuvant arthritis assay in rats than currently marketed nonsteroidal antiinflammatory drugs. Activity is maintained on reduction of these 2-(3-benzoylphenyl)propyl bulky amines to the corresponding alcohols or methylene analogues, on conversion of the ketone function to a primary amine or oxime, and on introduction of a 4-halo substitutent (Cl or F) on the terminal aromatic ring. Removal of the α-CH_3 group greatly reduces the antiiflammatory activity of the series. These compounds have been synthesized by the reductive amination of 2-(3-bromophenyl)propionaldehyde with the respective amine followed by lithiation of this product and condensation with the appropriate benzonitrile.

The literature in recent years is filled with reports of arylacetic acids that have shown significant antiinflammatory activity in animal models.[1] Unfortunately, many of these acids have exhibited considerable gastrointestinal intolerance in man. Consequently, the question was raised in our laboratories whether replacement of the acid moiety in the known clinically most active arylacetic acid structures by basic amine functions might not give compounds retaining the antiinflammatory activity of their acidic counterparts but with less incidence of gastrointestinal intolerance. This paper relates the synthesis and pharmacological properties of analogues of 2-(3-benzoylphenyl)propionic acid (Ketoprofen) where the carboxylic acid function has been replaced by a variety of amines. Many of these analogues exhibit potent antiinflammatory activity in both the carrageenan and adjuvant arthritis assays, limited gastrointestinal intolerance, low toxicity, and mild analgesic and antipyretic activities.

Chemistry. Preparation of the 2-(3-benzoylphenyl)-propylamines was most easily carried out by Scheme I. Conversion of 3-bromoacetophenone[2] to the corresponding propionaldehyde **42** proceeded via a Darzen's glycidic ester condensation. The appropriate amine and **42** were then reacted in benzene, water being azeotropically removed. The resulting enamines and imines were converted to their respective hydrochlorides and then reduced with sodium borohydride in DMF. Lithiation[3] of the distilled amines was followed either by reaction with an appropriate benzaldehyde or acetophenone (method B) to give alcohols **25** and **28–35** or by reaction with benzonitrile (method A) to give ketones **2**, **2a**, **3**, **5**, **6**, **8**, **10**, and **15–22** on acid hydrolytic workup. In some cases, the alcohols were oxidized to ketones **7** and **10** by using either chromium trioxide in sulfuric acid or a perchloric acid–nitric acid mixture in 1,2-dimethoxyethane[4] (methods C and D). Oximation of the ketones followed by reduction of the resulting oximes with sodium in ethanol (methods E and F) gave the corresponding amines **36–38**. Vinyl compound **39** was pre-

Scheme I



[a](1) $ClCH_2CO_2Et$, i-PrO$^-$; (2) NaOH; (3) H^+. [b](1) HN◯; (2) HCl; (3) $NaBH_4$. [c](1) n-BuLi; (2) $R_1C_6H_4CN$; (3) H^+. [d](1) n-BuLi; (2) C_6H_5CRO. [e]CrO_3,H_2SO_4 or HNO_3,$HClO_4$. [f]$NH_2OH.HCl$. [g]Na, EtOH. [h]H_2, Pd/C. [i]H^+.

(1) (a) Adams, S. S.; McCullough, K. F.; Nicholson, J. S. *Arch. Int. Pharmacodyn. Ther.* **1969**, *178*, 115. (b) Benslay, D. N. *Fed. Proc., Fed. Am. Soc. Exp. Biol.* **1971**, 30, 563. (c) Harrison, I. T.; Lewis, B.; Nelson, P.; Rooks, W.; Roszkowski, A.; Tomolonis, A.; Fried, J. H. *J. Med. Chem.* **1970**, *13*, 203.

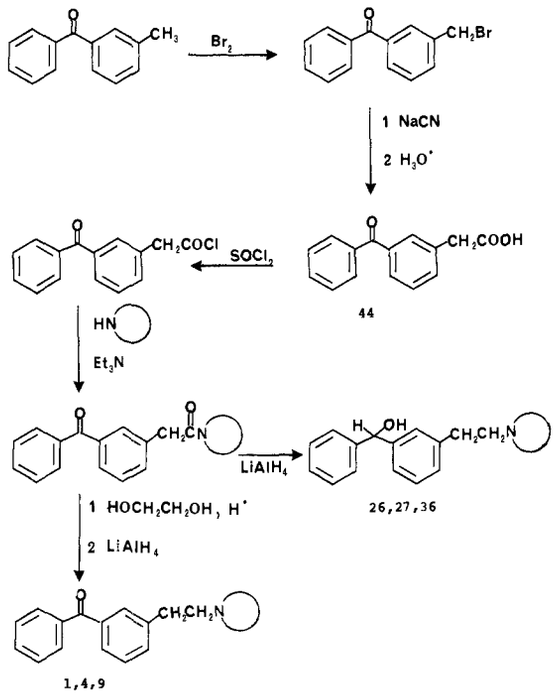
(2) Pearson, D. E.; Pope, H. W.; Hargrove, W. W. "Organic Synthesis"; Wiley: New York, 1960; Vol. 40, pp 7–10.

(3) Jones, R. G.; Gilman, H. "Organic Reactions"; Wiley: New York, 1951; Vol. 6, pp 352–3.

(4) McKillop, A.; Ford, M. *Synth. Commun.* **1972**, *2*, 307.

0022-2623/84/1827-1682$01.50/0

Scheme II



pared by acid-catalyzed elimination of water from alcohol **34** (method H). Catalytic reduction of the alcohols under acidic conditions (method G) gave the corresponding benzyl analogues **40** and **41**.

The desmethyl series of compounds were prepared in the manner depicted in Scheme II. Benzylic bromination of 3-methylbenzophenone gave the crude monobenzyl bromide in mixture with the unbrominated and dibrominated products. On treatment of the crude mixture with NaCN only the benzyl bromide reacted. Aqueous hydrolysis of the resulting nitrile gave a product from which the desired acid **44** could be readily separated. Conversion of **44** to the acid chloride with $SOCl_2$ followed by reaction with the appropriate amine gave the amides. These were either converted to the ketal and reduced with $LiAlH_4$ followed by hydrolysis to the ketones **1** and **4** (method I) or reduced directly with $LiAlH_4$ to give the amino alcohols **26–28** (method J) in moderate yield. In some cases, the limited yield was due to a significant amount of cleavage of the C–N bond.

The amines used for condensation with the propionaldehyde or acid chlorides were either available commercially or prepared by catalytic reduction of the corresponding unsaturated analogues.

Biological Results and Discussion

The testing results (see Table I) suggest several structural requirements for good antiinflammatory activity in the bulky amine series. In an admittedly limited number of examples an α-alkyl group at R_1 appears to be a necessary feature. Related compounds **1** and **2**, **9** and **10**, **27** and **28**, and **36** and **37** show little or no activity for the des-α-methyl member at the doses tested but excellent activity for the α-methyl analogue. This requirement has frequently been observed in other antiinflammatory arylacetic acid series such as naproxen,[1c] ibuprofen,[1a] and fenoprofen.[1b]

Substitution in the terminal aromatic ring also affects antiinflammatory activity. The placement of a methyl group in the 2-, 3-, or 4-position (**17**, **18**, **19**) greatly reduces or eliminates activity while the introduction of a 4-halo substituent (Cl and F) has an enhancing effect on antiinflammatory activity (**13**, **15** and **30**).

Varying the X substitution on the benzhydryl carbon while maintaining an α-methyl group, unsubstituted aromatic rings, and a cyclohexylmethylpiperidine group as constant structural features shows that whether X = O (**10**), NOH (**24**), OH, H (**28**), NH_2, H (**38**), or H, H (**40**), potent antiinflammatory activity is maintained. Much activity is lost, however, when X = CH_3, OH (**34**), CH_3, H (**41**), or CH_2 (**39**).

Alteration of the side-chain amine while maintaining the rest of the structure constant in the benzophenone series shows that practically all cyclic amines (**2**, **3**, **5**, **7**, **8**, **10**, **20–22**) show good activity. Only the activity of the smaller piperidine analogue **6** was in a range significantly less active than the rest.

The general antiinflammatory efficacy of these compounds vs. their ulcerogenic or toxic liabilities has been measured in two ways. In the first method using the 21-day adjuvant arthritis assay, the highest nonulcerogenic or toxic dose, i.e., less than 50% ulcer incidence or observed toxic response, is compared to the dose that results in a 50% inhibition of total hind paw volume changes. This measure, termed the relative safety index (Table II), indicates that, at least in rats, these compounds have a multifold advantage over some of the most commonly prescribed antiinflammatory drugs such as aspirin, indomethacin, ibuprofen, and phenylbutazone.

A second method for evaluating the efficacy of these compounds is by measuring the weight gain of the rats during the 21-day adjuvant arthritis test as a percent of the difference in weight gain between the positive, adjuvant arthritis, and negative control animals. The assumption is implicit that at least within a given series of compounds, the healthier animals, those least bothered by inflammatory manifestations or drug toxicity, will show a greater percentage weight gain, i.e., one more closely approximating that of the negative controls. As can be seen from Table II, rats treated with the bulky amines showed a high percentage of normal weight gain (80–90%) at the highest tolerated, effective dose. Rats treated with reference drugs, phenylbutazone (41%) and indomethacin (14%), have a much smaller percentage of normal weight gain at the highest tolerated doses.

A comparison of the relative potency of the bulky amines and other standard drugs as presented in Table II shows that the bulky amines are 3–12 times more potent than phenylbutazone (PHB). Ibuprofen is much less potent, 0.05 times PHB, while ketoprofen 32 times PHB and indomethacin, 30 times PHB, are more potent.

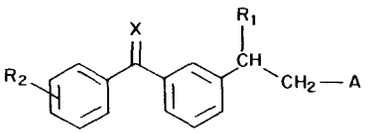
Other general findings show that compounds **2a** and **10**, the only bulky amines looked at in the guinea pig UV erythema test,[5] are, when administered by gavage, active at doses of 0.03 and 0.09 mmol/kg. The relative activities in this test were similar to those seen in the adjuvant testing, i.e., bulky amines showing activity greater than phenylbutazone and less than ketoprofen and indomethacin.

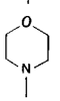
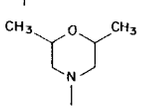
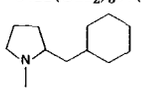
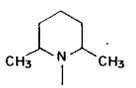
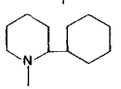
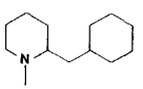
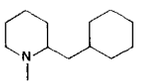
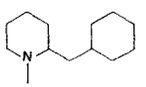
Compounds **2a** and **10** have been tested orally in the acetylcholine writhing test[6] in mice and were found to elicit analgesic activity. Compound **2a** has an ED_{50} of 8.4 mg/kg and **10** an ED_{50} of 55 mg/kg while the standard, ketoprofen, exhibits an ED_{50} of 2 mg/kg in this model.

The morpholino analogue **2a** is a very weak inhibitor ($IC_{50} = 1 \times 10^{-5}$ M) of prostaglandin synthetase. This was

(5) Winder, C. V.; Wax, J.; Burr, V.; Been, M.; Rosiere, C. E., *Arch. Int. Pharmacodyn. Ther.* **1958**, *116*, 261.
(6) Collier, H. O. J.; Dinneen, L. C.; Johnson, C. A.; Schneider, C. *Br. J. Pharmacol. Chemother.* **1968**, *32*, 295.

Table I. Antiinflammatory Activity of Some 2-(3-Benzoylphenyl)propylamines and Their Derivatives



no.	X	A	R_1	R_2	mp, °C	formula	anal.[a]	% yield[b]	method	carrageenin edema assay[c]	std adjuvant arthritis assay[d]
1	O		H	H	177.5–180	$C_{19}H_{21}NO_2 \cdot HCl \cdot H_2O$	C, H, Cl	66	I	+	+
2	O		CH_3	H	oil	$C_{20}H_{23}NO_2$	C, H, N	48	A	+++	++++++
2a	O		CH_3	H	151–153	$C_{20}H_{23}NO_2 \cdot HCl \cdot H_2O$	C, H, Cl	71	A	+++	++++++
3	O		CH_3	H	156–158	$C_{22}H_{27}NO_2 \cdot C_6H_{13}NO_3S$	C, H, S	27	A	000000	+++++
4	O	$-NH(CH_2)_3N(CH_3)_2$	H	H	194–197	$C_{20}H_{26}N_2O \cdot 2HCl \cdot {}^1/_2H_2O$	C, H, Cl	11	I	000	++
5	O		CH_3	H	oil	$C_{27}H_{35}NO$	C, H, N	48	A	0000	0.16–70%
6	O		CH_3	H	amorphous solid	$C_{21}H_{25}NO \cdot HCl$	C, H, Cl[e]	28	A	000	++
7	O		CH_3	H	oil	$C_{23}H_{29}NO$	C, H, N	29	C	00000	0.06–78%
8	O		CH_3	H	oil	$C_{27}H_{35}NO$	C, H, N	45	A	000	+++++++
9	O		H	H	oil	$C_{27}H_{35}NO$	C, H, N	63	D	++	NT[g]
10	O		CH_3	H	oil	$C_{28}H_{37}NO$	C, H, N	61	C	+++	++++++
								55	D		
								69	A		
11	O		CH_3	2-Cl	oil	$C_{28}H_{36}ClNO$	C, H, N	41	D	+++	+++++

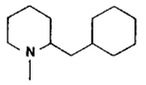
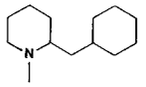
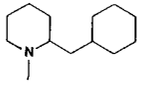
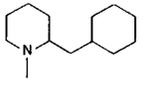
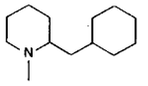
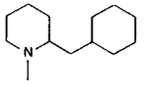
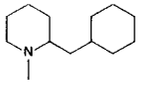
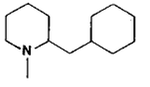
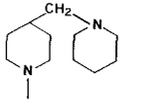
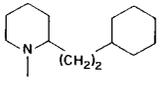
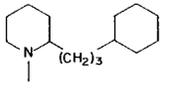
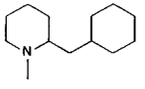
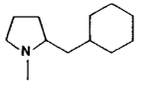
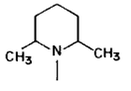
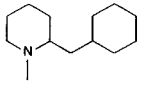
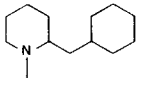
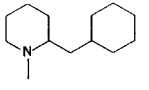
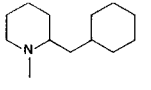
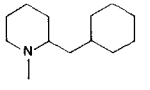
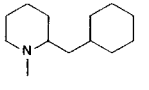
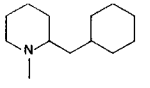
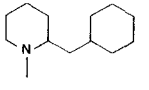
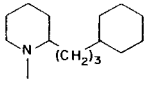
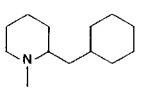
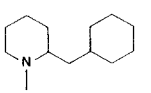
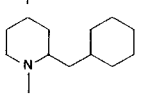
12	O		CH_3	3-Cl	oil	$C_{28}H_{36}ClNO$	C, H, N	56	D	+	NT[g]
13	O		CH_3	4-Cl	oil	$C_{28}H_{36}ClNO$	C, H, Cl	65	D	+++++	0.02–90% toxic
14	O		CH_3	3,4-Cl_2	oil	$C_{28}H_{35}Cl_2NO$	C, H, N	44	D	+	NT[g]
15	O		CH_3	4-F	oil	$C_{28}H_{36}FNO$	C, H, N	23	A	+++	++++++
16	O		CH_3	4-OCH_3	oil	$C_{29}H_{39}NO_2$	C, H, N	32	A	++	++++
17	O		CH_3	2-CH_3	oil	$C_{29}H_{39}NO$	C, H, N	23	A	++	NT[g]
18	O		CH_3	3-CH_3	oil	$C_{29}H_{39}NO$	C, H, N	51	A	+	NT[g]
19	O		CH_3	4-CH_3	oil	$C_{29}H_{39}NO$	C, H, N	43	A	+	NT[g]
20	O		CH_3	H	267–270	$C_{27}H_{36}N_2O \cdot 2HCl$	C, H, N	45	A	0000	+++++++
21	O		CH_3	H	oil	$C_{29}H_{39}NO$	C, H, N	51	A	000	+++++++
22	O		CH_3	H	oil	$C_{30}H_{41}NO$	C, H, N	48	A	000	0.16–100%
23	=NOH		H	H	117–134	$C_{19}H_{22}N_2O_2$	C, H, N	87	E	+	+
24	=NOH		CH_3	H	glass	$C_{28}H_{38}N_2O$	C, H, N	96	E	++++	+++++++
25	H, OH		CH_3	H	oil	$C_{27}H_{37}NO$[f]	C, H, N	38	B	0	0.16–91%
26	H, OH		H	H	115–117	$C_{22}H_{29}NO$	C, H, N	20	J	+	+++

Table I (Continued)

no.	X	A	R_1	R_2	mp, °C	formula	anal.[a]	% yield[b]	method	carrageenin edema assay[c]	std adjuvant arthritis assay[d]
27	H, OH		H	H	122–124	$C_{27}H_{37}NO$	C, H, N	42	J	+	NT[g]
28	H, OH		CH_3	H	oil	$C_{28}H_{39}NO$	C, H, N	82	J	+++	+++++++
29	H, OH		CH_3	3-Cl	oil	$C_{28}H_{38}ClNO$	C, H, N	23	B	+	NT[g]
30	H, OH		CH_3	4-Cl	oil	$C_{28}H_{38}ClNO$	C, H, Cl	75	B	++++	++++++
31	H, OH		CH_3	2,6-Cl_2	oil	$C_{28}H_{37}Cl_2NO$	C, H, Cl	81	B	+	NT[g]
32	H, OH		CH_3	4-OCH_3	oil	$C_{29}H_{41}NO_2$	C, H, N	47	B	+	+
33	H, OH		CH_3	4-CH_3	oil	$C_{29}H_{41}NO$	C, H, N	76	B	+	NT[g]
34	CH_3, OH		CH_3	H	oil	$C_{29}H_{41}NO$	C, H, N	47	B	+	NT[g]
35	H, OH		CH_3	H	oil	$C_{30}H_{43}NO$	C, H, N	21	B	+++	NT[g]
36	H, NH_2		H	H	260–263	$C_{19}H_{24}N_2O \cdot 2HCl$	C, H, N	89	F	+	+
37	H, NH_2		CH_3	H	glass	$C_{20}H_{26}N_2O \cdot 2HCl$	C, H, Cl	59	F	0000	+++++
38	H, NH_2		CH_3	H	167–195	$C_{28}H_{40}N_2 \cdot 2HCl$	C, H, N, Cl	45	F	+++	+++++++
39	$=CH_2$		CH_3	H	oil	$C_{29}H_{39}N$	C, H, N	79	H	0000	NT[g]
40	CH_2		CH_3	H	oil	$C_{28}H_{39}N$	C, H, N	86	G	++	+++++++

41	H, CH_3		CH_3	H	oil	$C_{29}H_{41}N$	C, H, N	80	G	+	+
Ketoprofen									++++++		0.009–82%
ibuprofen									000		0.139–40%
phenylbutazone									0000		++++

[a] Analyses fall within the theoretical limits ±0.4% for the elements described. [b] Yield on final step. [c] Carrageenin paw edema (rat) percent inhibition of edema, at 0.02 mmol/kg 0–19 +, 20–29 ++, 30–39 +++, 40–49 ++++, 50–59 +++++, 60–69 ++++++ at 0.08 mmol/kg 0–19 0, 20–29 00, 30–39 000, 40–49 0000, 50–59 00000, 60–69 000000. [d] Adjuvant arthritis (rat) percent inhibition of total paw volume at 0.08 mmol/kg 0–39 +, 40–49 ++, 50–59 +++, 60–69 ++++, 70–79 +++++, 80–89 ++++++, 90–99 +++++++; where values were obtained at nonstandard doses, results are recorded as follows: dose mmol/kg, percent inhibition of total paw volume. [e] C: calcd, 73.34; found, 72.70. [f] C, H: calcd 82.81, 9.52; found 82.29, 10.03. [g] NT = not tested.

shown by the classical method of studying [^{14}C]arachidonic acid conversion to prostaglandins using prostaglandin synthetase from bull seminal vesicles. In comparison the activity of indomethacin ($IC_{50} = 8 \times 10^{-7}$ M) was 12.5 times that of **2a** and ketoprofen ($IC_{50} = 2 \times 10^{-7}$ M) was 50 times that of **2a** in this test.

Compound **10** administered orally also shows antipyretic properties.[7] It has significant activity at 37 mg/kg but was not tested at lower dose levels.

Ultimately, compound **2a**, the hydrochloride salt of the morpholino base analogue, was chosen for advanced evaluation because of its high antiinflammatory activity as shown by the carrageenin edema assay and the adjuvant arthritis assay and its potential usefulness as a mild analgesic as demonstrated by its activity in the acetylcholine writhing test. This compound was also more easily synthesized and possessed physical properties that were amenable to drug formulation.

Experimental Section

Melting points, determined in open capillary tubes with a Meltemp apparatus, are uncorrected. Analyses, performed by Albro testing laboratory, East Greenbush, NY, fell within the theoretical limits ±0.4% for the elements described. All column chromatography on alumina utilized Fisher A-540 adsorption alumina (80–200 mesh). NMR spectra were determined on all compounds with a Varian A-60 or Varian HA-100 instrument using Me_4Si as internal standard and were consistent for the described products.

2-(3-Bromophenyl)propanal (42). A solution of sodium isopropoxide, 60 g (2.6 mol) of Na in 2200 mL of *i*-PrOH, was cooled to 7 °C and treated over 30 min with 318 g (1.6 mol) of 3-bromoacetophenone[2] and 352 g (2.88 mol) of ethyl chloroacetate. The resulting mixture was stirred at 7 °C for 5 h and room temperature for 48 h, heated at reflux for 1 h, and distilled to remove approximately 1 L of *i*-PrOH and the residue diluted with 1900 mL of H_2O and 1200 mL toluene. The layers were separated, and the aqueous phase was reextracted with toluene. The toluene extracts were washed with brine, dried, and evaporated to yield 558 g of crude glycidic ester. This product was heated at reflux for 2 h in a basic solution (70 g of NaOH, 225 mL of H_2O, 1200 mL of EtOH); the resulting mixture was taken to dryness in vacuo to yield 576 g of a solid, which was dissolved in H_2O and acidified with dilute HCl, and the mixture was extracted with C_6H_6. The C_6H_6 extracts were evaporated, and the residue was steam distilled to yield 273 g (80%). This product contains about 10% of the starting ketone but is pure enough for the next step. The pure aldehyde **42** may be obtained by preparation of the bisulfite addition complex, cleavage of same with 10% Na_2CO_3, followed by ether extraction. Anal. (C_9H_9BrO) C, H, Br.

2-(Cyclohexylmethyl)-1-[2-(3-bromophenyl)propyl]-piperidine (43). A solution of 300 g (1.4 mol) of aldehyde **42** and 510 g (2.82 mol) of 2-(cyclohexylmethyl)piperidine in 6 L of C_6H_6 was heated at reflux under a Dean–Stark trap for 18 h. The solvent was removed in vacuo and the resulting oil distilled to remove lower boiling products. The resulting higher boiling products, 490 g, were dissolved in 3 L of hexane; this solution was ice cooled and made acidic with ethereal HCl to give a white gummy solid, which was filtered and washed with Et_2O. This crude, crystalline iminium hydrochloride was dissolved in 3.5 L of DMF and the cooled solution was treated portionwise over 45 min with 85 g (2.2 mol) of $NaBH_4$. The mixture was stirred for 1 h, then treated with 1 L of 10% NaOH solution and 6 L of H_2O, and extracted with hexane. The hexane layers were washed with brine, dried, and evaporated in vacuo to give an oil, which on vacuum distillation gave 429 g (87%) of **43** as an oil, bp 150–157 °C (0.1 mm). Anal. ($C_{21}H_{32}BrN$) C, H, Br.

2-(3-Benzoylphenyl)acetic Acid (44). A solution of 120 g (0.61 mol) of 3-methylbenzophenone in 240 mL of $BrCH_2CH_4Br$ was heated at reflux and treated over 2.75 h with a solution of 101 g (0.63 mol) of Br_2 in 72 mL of $BrCH_2CH_2Br$. After addition,

(7) Pyrexia was induced in rats by subcutaneous injection of bakers' yeast.

Table II. Antiinflammatory and Ulcerogenic Activities of 2-(3-Benzoylphenyl)propylamines and Derivatives and Standard Drugs (Measured in a 21-Day Adjuvant Arthritis (AA) Assay)

compd	dose, mmole/kg (mg)	% of normal body wt gain po for 3-wk dosing period[a]	AA (21-day medication) %inhibn of paw vol	ED_{50}, mmol/kg (mg)	rel potency to phenylbutazone (95% conf limits)	ulcerogenicity: 21-day medication AA test, animals with ulcers/animals in test		rel safety index[b]
						intestinal	gastric	
2	0.08 (24.7)	66	82	0.008 (2.5)	8.6 (3.3–44.7)	1/8	0/8	20
	0.16 (49.4)					3/8	1/8	
2a	0.005 (1.82)	2	49	0.005 (1.8)				4
	0.02 (7.28)	10	72					
	0.08 (29.1)	43	89			5/8	0/8	
	0.16 (58.2)	70				4/8	2/8	
	0.32 (116.4)	46				7/7	1/7	
10	0.005 (2.02)	27	56[c]	0.003 (1.2)	8.7			27
	0.02 (8.07)	55	79[c]			1/4	0/4	
	0.08 (32.3)	82	90[c]			4/15[c]	1/15[c]	
	0.16 (64.6)					toxic		
13	0.005 (2.19)	34	62	0.003 (1.3)	11.9 (6.4–29.2)			7[d]
	0.02 (8.76)	89	90			0/8	0/8	
	0.08 (35.0)					toxic		
15	0.005 (2.11)	50	61	0.003 (1.26)				
	0.02 (8.43)	31	55			1/4	0/4	27
	0.08 (33.7)	81	85			3/8	1/8	
	0.16 (67.4)					toxic		
28	0.005 (2.03)	13	37					
	0.02 (8.11)	36	82	0.008 (3.2)	8.6 (3.3–44.7)			10[d]
	0.08 (32.4)	67	110			1/8	1/8	
	0.32 (130)					3/3	1/3	
30	0.005 (2.20)	40	64	0.001 (0.44)				
	0.02 (8.80)	69	70					
	0.08 (35.2)	87	88			1/4	0/4	80
	0.16 (70.4)	84				3/4	0/4	
	0.32 (141)					toxic		
Ketoprofen	0.006 (0.152)	21	31	0.001 (0.25)	32.4 (17.8–70.6)			
	0.002 (0.51)	35	68			0/4	0/4	
	0.009 (2.29)	79	82			4/24[c]	6/24[c]	9[d]
	0.03 (7.62)					22/31[c]	3/31[c]	
	0.06 (15.2)					toxic		
phenylbutazone	0.08 (24.6)	21[c]	66[c]	0.04 (12.3)		11/72[c]	14/72[c]	
	0.41 (126)					2/8	3/8	10
	0.50 (154)	41[c]				36/55[c]	17/55[c]	
	0.82 (253)							
indomethacin	0.0014 (0.50)	14[c]	63[c]	0.0004 (0.14)	20.0 (7.0–44.3)	3/32[c]	6/32[c]	4[d]
	0.008 (2.86)	48[c]				17/30[c]	5/30[c]	
	0.011 (3.94)	38						
ibuprofen	0.139 (28.6)		40					
	0.278 (57.2)	1	56	0.21 (43.3)	0.049 (0.019–0.11)	2/4	0/4	1
	0.55 (113)	18	79			7/8	2/8	
	0.97 (200)					4/4	0/3	

[a] % = (drug treated animal) − (positive control)/(negative control) − (positive control) × 100. [b] Highest nonulcerogenic dose (less than 50% ulcer incidence) ÷ ED_{50}. [c] Values obtained are the summation of several test runs. [d] The relative safety index value may be somewhat larger than this value and is not directly comparable to the other listed values that were determined at 2-fold dose increases.

heating was continued for another 0.5 h. The solvent was then removed in vacuo, giving 181 g of an oil, which was dissolved in 480 mL of dioxane. This solution was treated with a solution of 86 g (1.75 mol) of sodium cyanide in 240 mL of H_2O and the resulting solution heated at reflux for 2.75 h. A portion (300 mL) of the solution was then removed in vacuo and the rest was poured into H_2O and extracted with CH_2Cl_2. The CH_2Cl_2 extracts were washed with H_2O, dried (Na_2SO_4), and evaporated to give 150 g of an oil. This oil was mixed with 150 mL of HOAc, 150 mL of H_2O, and 150 mL of concentrated H_2SO_4 and heated at reflux for 3 h. The mixture was cooled and a precipitate collected, washed with H_2O, and dissolved in 600 mL of 5% NaOH solution. The basic solution was extracted with ether, treated with Darko, filtered, and acidified with 6 N HCl to give 77.2 g (53%) of 44, mp 107–110 °C (lit.[8] mp 115 °C).

Method A. [3-[2-[2-(Cyclohexylmethyl)-1-piperidinyl]-1-methylethyl]phenyl]phenylmethanone (10). A solution of 75 g (0.198 mol) of **43** in 400 mL of Et_2O was cooled to 5 °C and treated over 5 min with 384 mL of 0.98 M (0.376 mol) *n*-BuLi in Et_2O. The resulting solution was stirred at 5–10 °C for 0.5 h and to room temperature over 1 h, heated at reflux for 0.5 h, and cooled to 5 °C and a solution of 43 g (0.42 mol) of benzonitrile then added over 20 min. It was stirred at 5 °C for 2.5 h, allowed to sit at room temperature overnight, and treated the next morning with 270 mL of an acid solution (15 mL of concentrated H_2SO_4, 75 mL of H_2O, 180 mL of dioxane) with cooling. The reaction was then heated at reflux for 2 h, cooled, made basic with 10% KOH solution, and extracted with Et_2O. The Et_2O extracts were washed with brine, dried (Na_2SO_4), and evaporated in vacuo (first with low vacuum and then high vacuum), giving 92.3 g of an oil, which was chromatographed on 1600 g of alumina with hexane–Et_2O (9:1) as eluant, yielding 54.9 g (69%) of **10**.

Method B. α-(4-Chlorophenyl)-3-[2-[2-(cyclohexylmethyl)-1-piperidinyl]-1-methylethyl]benzenemethanol (30). A solution of **43**, 18.9 g (0.05 mol in 90 mL of Et_2O), was cooled to 10 °C and treated over 5 min with 95 mL of 1.08 M *n*-BuLi in Et_2O. The resulting solution was stirred at $t < 10$ °C for 45 min and room temperature for 1 h, heated at reflux for 0.5 h, and then recooled to $t < 5$ °C. A solution of 4-chlorobenzaldehyde, 15.5 g (0.11 mol) in 50 mL of Et_2O, was added over 5 min; the resulting solution was stirred at $t < 10$ °C for 0.5 h and to room

(8) Allais, A.; Rousseau, G.; Meier, J.; Deraedt, R.; Benzoni, J.; Chifflot, L. *Eur. J. Med. Chem.* **1974**, *9*, 381.

temperature for 0.5 h, heated at reflux for 0.5 h, cooled to 10 °C, and treated with 70 mL of 10% NaOH solution. After stirring of this mixture for 10 min, the layers were separated, the aqueous phase was reextracted with Et_2O, and the Et_2O extracts were washed with brine and dried (Na_2SO_4). Evaporation of the solvent in vacuo gave 35.4 g of an oil. A solution of this oil in 90 mL of MeOH was cooled to 10 °C and treated with 4.5 g of $NaBH_4$;[9] this mixture was stirred for 30 min at $t < 15$ °C and then treated cautiously with 90 mL of 4 N H_2SO_4, diluted with a little additional MeOH–H_2O to obtain a solution, and extracted four times with hexane to remove nonbasic impurities. The aqueous solution was basified with 10% NaOH solution and extracted with hexane. These hexane extracts were washed with brine, dried (Na_2SO_4), and evaporated in vacuo to give 24.7 g of an oil, which was chromatographed on 600 g of alumina with an eluant of 1.75% *i*-$PrNH_2$ in hexane to give 16.6 g (75%) of **30**.

Method C. Compound 10. A solution of 26.8 g (0.066 mol) of **28** in 140 mL of C_6H_6 was vigorously stirred, cooled to 15 °C, and treated over 10 min with 58 mL of a CrO_3 solution (26.7 g of CrO_3 in 23 mL of concentrated H_2SO_4, diluted with H_2O to 100 mL). The reaction was stirred at room temperature for 1.75 h with the aid of occasional ice-bath cooling. The C_6H_6 layer was separated and the aqueous phase made strongly basic with 120 mL of 10% NaOH solution and reextracted with C_6H_6. The C_6H_6 extracts were washed with 5% NaOH solution and brine and dried (Na_2SO_4). Evaporation of solvent in vacuo gave 21.8 g of an oil, which was chromatographed on 300 g of alumina with 3% *i*-$PrNH_2$ in hexane as eluant, yield 16.2 g (61%) of **10**.

Method D. (4-Chlorophenyl)[3-[2-[2-(cyclohexylmethyl)-1-piperidinyl]-1-methylethyl]phenyl]methanone (13). A solution of 13.2 g (0.03 mol) of **30** in 188 mL of an acid solution (150 mL of 1,2-dimethoxyethane, 16 mL of concentrated HNO_3, 32 mL of 50% $HClO_4$) was heated at reflux for 1.25 h. It was then cooled to 10 °C diluted with 50 mL of H_2O, made basic with 10% NaOH, diluted with a little MeOH to obtain a solution, and extracted with hexane. The hexane extracts were washed with H_2O and brine and dried (Na_2SO_4). Evaporation of solvent gave 12 g of an oil, which was chromatographed on 200 g of alumina with hexane–Et_2O (9:1) as eluant, yield 8.44 g (65%) of **13**.

Method E. [3-[2-[2-(Cyclohexylmethyl)-1-piperidinyl]-1-methylethyl]phenyl]phenylmethanone Oxime (24). A mixture of 37.5 g (0.093 mol) of **10** and 10 g of $NH_2OH·HCl$ in 125 mL of 95% EtOH and 25 mL of H_2O was stirred and treated with 19.4 g of powdered NaOH, added in small portions. The resulting mixture was stirred and heated at reflux for 0.5 h, cooled, and diluted with hexane, and the aqueous layer was separated. The hexane layer was washed with brine and dried (Na_2SO_4). Evaporation of solvent gave 41.6 g of an oil, which was chromatographed on 800 g of alumina with hexane–Et_2O (7:3) as eluant, yield 37.3 g (96%) of **24**.

Method F. 3-[2-[2-(Cyclohexylmethyl)-1-piperidinyl]-1-methylethyl]-α-phenylbenzenemethanamine Dihydrochloride (38). A solution of 17 g (0.041 mol) of **24** in 110 mL of EtOH was heated to reflux and treated with 10 g (0.43 mol) of sodium metal added in small pieces. Heating at reflux was continued until all the sodium had dissolved. The solution was then cooled, diluted with 140 mL of H_2O, evaporated to a volume of 150 mL in vacuo, and extracted three times with C_6H_6. Evaporation of the C_6H_6 gave 14.2 g of an oil, which was converted in $CHCl_3$ to the acetate salt with HOAc. The salt was chromatographed on 500 g of alumina with $CHCl_3$ as eluant and gave 12.7 g of the free base. This was dissolved in ethanol, treated with ethanolic HCl, and evaporated to dryness to give 12.5 g (45%) of **38**.

Method G. 2-(Cyclohexylmethyl)-1-[2-methyl-2-[3-(1-phenylethyl)phenyl]ethyl]piperidine (41). A mixture of 11.1 g (0.027 mol) of **34** in 180 mL of HOAc and 20 mL of 72% $HClO_4$ with 0.8 g of Pd/C catalyst was hydrogenated on a Parr apparatus at 35 psi for 2.5 h. The catalyst was filtered off, the solvent evaporated, and the residue dissolved in MeOH and basified with 10% NaOH solution, and this solution was extracted with hexane. The hexane solution was extracted with an acid solution (36 mL of MeOH, 32 mL of H_2O, and 4 mL of concentrated H_2SO_4). These acid extracts were made basic with 10% NaOH solution and extracted with hexane. The hexane extracts were dried (Na_2SO_4) and evaporated to give 9.3 g of an oil, which was chromatographed on 200 g of alumina with hexane–Et_2O (8:2) as eluant, yield 8.0 g (80%) of **41**.

Method H. 2-(Cyclohexylmethyl)-1-[2-[3-(1-phenylethenyl)phenyl]propyl]piperidine (39). A solution of 13.0 g (0.031 mol) of **34** in 130 mL of MeOH containing 3 mL of concentrated H_2SO_4 was stirred and heated at reflux for 0.75 h, then cooled, diluted with 100 mL of H_2O and 5 mL of 35% NaOH solution, and extracted with hexane. The hexane extracts were washed with brine and dried (Na_2SO_4). Evaporation of solvent gave 14.2 g of an oil, which was chromatographed on 260 g of alumina with hexane–Et_2O (92.8) as eluant, yield 9.4 g (79%) of **39**.

Method I. [3-[2-(4-Morpholinyl)ethyl]phenyl]phenylmethanone Hydrochloride Monohydrate (1). A solution of 49 g (0.158 mol) of 4-[2-(3-benzoylphenyl)-1-oxoethyl]morpholine, 1250 mL of C_6H_6, 125 mL of ethylene glycol, and 2.5 g of *p*-toluenesulfonic acid was heated overnight at reflux with a Dean–Stark trap in place. The reaction solution was then cooled, washed with 5% $KHCO_3$ and brine, dried (Na_2SO_4), and evaporated to give 58.6 g of an oil. This oil in 570 mL of Et_2O was added over 25 min to an ice cooled and stirred slurry of $LiAlH_4$ in 280 mL of Et_2O. After addition, stirring was continued cold for 0.5 h and then at room temperature for 2.5 h. The mixture was recooled, treated with 12 mL of H_2O, 12 mL of 15% KOH solution, and 36 mL of H_2O, and stirred for 20 min. The Li salts were removed by filtration, and the filtrate was evaporated to give 50 g. This product was stirred with 300 mL of 1.5 N hydrochloric acid for 0.75 h at 55–60 °C, then cooled, and treated with 25 mL of concentrated HCl and 50 mL of Et_2O. The resulting precipitate was filtered, washed with Et_2O, and recrystallized from 1200 mL of acetone to yield 35 g (66%) of **1**.

Method J. α-Phenyl-3-[2-(2,6-dimethyl-1-piperidinyl)ethyl]benzenemethanol (26). A solution of 77.2 g (0.32 mol) of 2-(3-benzoylphenyl)acetic acid (**44**) in 120 mL of C_6H_6 and 64 g (0.54 mol) of $SOCl_2$ was heated at reflux for 2.25 h. C_6H_6 and $SOCl_2$ were removed in vacuo and additional C_6H_6 was added two more times and evaporated to yield 83.8 g of the acid chloride. A 42-g (0.16 mol) portion of the acid chloride in 60 mL of Et_2O was added over 15 min to an ice-cooled solution of 19.8 g (0.175 mol) of 2,6-dimethylpiperidine and 19.4 g (0.192 mol) of triethylamine in 150 mL of Et_2O. The reaction was stirred at room temperature for 48 h. A gum formed and the Et_2O was decanted away from it. The Et_2O was washed twice with 3 N HCl and once with brine and dried (Na_2SO_4). Evaporation of the Et_2O yielded 21 g of an oil. The gum was washed with H_2O and dissolved in $CHCl_3$. The $CHCl_3$ solution was washed twice with 3 N HCl and then combined with the 21 g of oil obtained from the Et_2O extracts. This solution was washed with 10% Na_2CO_3 and dried (Na_2SO_4). Evaporation of solvent gave 50 g.

A mixture of 13.9 g (0.365 mol) of $LiAlH_4$ in 300 mL of Et_2O was stirred and cooled at $t < 10$ °C while a mixture of 49 g (0.146 mol) of the crude amide in 700 mL of Et_2O was added over 20 min. Benzene (25 mL) was used to dissolve and wash in residual amide. The mixture was stirred at room temperature for 3.5 h and then treated sequentially with 14 mL of H_2O, 14 mL of 15% NaOH, and 42 mL of H_2O. The resulting mixture was stirred for 1 h and filtered. The filtrate was evaporated and gave 37.3 g of an oil, which on slurrying with Et_2O gave 6.06 g of the desired amine. The mother liquors from this product were evaporated and chromatographed on 800 g of alumina with hexane–Et_2O–*i*-$PrNH_2$ (68:30:2) as eluant, yield 7.6 g. The two products were combined and recrystallized from 75 mL of C_6H_6 and 30 mL hexane to give 9.52 g (20%) of **26**.

General Procedure. Reduction of Unsaturated Amines. 2-(2-Cyclohexylethyl)piperidine Hydrochloride. A mixture of 9.1 g (0.05 mol) of 2-stilbazole,[10] 1 g of PtO_2, 10 mL of concentrated HCl, and 240 mL of EtOH was shaken under 55 psi

(9) Some of the alcohol is converted to the ketone in the earlier part of the reaction procedure. The $NaBH_4$ reduction reconverts this to the alcohol.

(10) Shaw, B. D.; Wagstaff, E. A. *J. Chem. Soc.* **1933**, 77.

of H_2 at 60 °C on a Parr apparatus for 8 h. The catalyst was removed by filtration and the filtrate was concentrated to 50 mL and then diluted with 200 mL of acetone. The resulting hydrochloride salt, 9.6 g, was filtered.

Biological Methods. Carrageenin Edema Assay. Male rats (Charles River, Sprague–Dawley strain) weighing 100–110 g were divided into groups of eight, fasted for 18 h, and administered by gavage, a placebo, or the drug suspended in 1% gum tragacanth or in a corn oil–water emulsion. One hour after medication, 0.05 mL of a 1% suspension of carrageenin in 0.9% saline was injected into the plantar tissue of the left hind paw. Three hours later, the increase in paw volume (difference between the left hind paw and the uninjected right hind paw) was measured by mercury displacement. The mean increase in paw volume was compared between drug treated groups and placebo to calculate the percent inhibition.

Standard Adjuvant Arthritis Assay. Male rats (Charles River, Sprague–Dawley strain) weighing 200–230 g in groups of eight had adjuvant (*M. butyricum*) 0.1 mL of a 0.6% suspension in heavy mineral oil or a mineral oil placebo, injected into the plantar tissue of one hind paw. Nine days after adjuvant injection, a 12-day daily medication by gavage routine was begun. The test compound was suspended in 1% gum tragacanth or in a corn oil–water emulsion. Negative control and adjuvant injected control animals received the vehicle only. Twenty-four hours after the last medication, the animals were weighed, and the increase in total hind paw volume was determined by mercury displacement. The percent inhibition was calculated from the average differences in hind paw volume between the adjuvant injected controls and the adjuvant-injected medicated rats.

Adjuvant Arthritis Assay. 21-Day Medication. The procedure was similar to the standard adjuvant arthritis assay except that medication was begun on the day of adjuvant injection. At the conclusion of the experiment, the animals were weighed, total hind paw volume was measured by mercury displacement, and the animals were sacrificed. The small intestines and stomachs of the animals were examined for ulceration.

Registry No. 1, 92365-90-7; 1·HCl, 60695-27-4; **2**, 60695-51-4; **2a**, 60695-54-7; **3**, 60695-55-8; **3**·$C_6H_{13}NO_3S$, 60695-56-9; **4**, 92365-91-8; 4·2HCl, 60695-28-5; **5**, 60695-41-2; **6**, 92365-92-9; **6**·HCl, 81598-09-6; **7**, 60695-63-8; **8**, 60695-46-7; **9**, 60695-78-5; **10**, 60695-62-7; 11, 60695-81-0; **12**, 60695-79-6; **13**, 60695-77-4; **14**, 60695-80-9; **15**, 60695-43-4; **16**, 60991-10-8; **17**, 60695-59-2; **18**, 60695-60-5; **19**, 60695-44-5; **20**, 92365-93-0; **20**·HCl, 81311-09-3; **21**, 60695-48-9; **22**, 60695-45-6; **23**, 60695-64-9; **24**, 60695-68-3; **25**, 60695-34-3; **26**, 60695-25-2; **27**, 60695-24-1; **28**, 60695-22-9; **29**, 60695-33-2; **30**, 60695-39-8; **31**, 60731-07-9; **32**, 60695-32-1; **33**, 60695-38-7; **34**, 60695-40-1; **35**, 60695-37-6; **36**, 92365-94-1; **36**·2HCl, 60695-69-4; **37**, 92365-95-2; **37**·2HCl, 60695-71-8; **38**, 92365-96-3; **38**·2HCl, 60695-67-2; **39**, 60695-72-9; **40**, 60695-61-6; 41, 60731-06-8; **42**, 59452-90-3; **43**, 60601-82-3; 44, 22071-22-3; 3-bromoacetophenone, 2142-63-4; ethyl chloroacetate, 105-39-5; ethyl 3′-bromo-3-methyl-2,3-epoxybenzenepropanoic acid, 81606-42-0; 2-(cyclohexylmethyl)piperidine, 51523-49-0; 3-methylbenzophenone, 643-65-2; 3-(bromomethyl)benzophenone, 22071-24-5; 3-(cyanomethyl)benzophenone, 21288-34-6; benzonitrile, 100-47-0; 4-chlorobenzaldehyde, 104-88-1; *p*-chloro-*m*′-[2-[2-(cyclohexylmethyl)-1-piperidinyl]-1-methylethyl]benzophenone, 60695-77-4; 4-[2-(3-benzoylphenyl)-1-oxoethyl]morpholine, 81597-82-2; 3-(2-chloro-2-oxoethyl)benzophenone, 41652-38-4; 2,6-dimethylpiperidine, 504-03-0; *N*-[2-(3-benzoylphenyl)acetyl]-2,6-dimethylpiperidine, 92365-98-5; 3-[2-morpholino-2-oxoethyl]-benzophenone cyclic ethylene acetal, 92365-97-4.

Azasteroids as Inhibitors of Rat Prostatic 5α-Reductase

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A series of A-ring heterocyclic steroids has been prepared and tested for inhibition of rat prostatic steroid 5α-reductase in vitro. Strikingly high inhibitory activity was found with a group of 17β-substituted 4-methyl-4-aza-5α-androstan-3-ones. These compounds were prepared from 3-keto-Δ^4-precursors by oxidative (O_3 or $NaIO_4$–$KMnO_4$) A-ring cleavage followed, in turn, by ring closure with an amine and hydrogenation over platinum catalyst. Other A-ring azasteroids were made by Beckmann rearrangement of oximes of 2-oxo-*A*-nor-, 3-oxo- and 4-oxo-5α-androstanes. An *A*-nor-2-oxo-3-azasteroid was prepared by oxidative decarbonylation of a precursor 2,3-dioxo-4-azasteroid with *m*-chloroperbenzoic acid. A-ring modifications of the 4-azasteroids included Δ^1-unsaturation, 2- and 4-substituents, and 3-carbonyl replacements. Side chains at the 17-position were varied with an emphasis on carboxylate derivatives (salts, esters, and amides).

The enzyme 5α-reductase serves an important function in many androgen-sensitive cells by converting the major circulating androgenic hormone, testosterone (T) irreversibly into the more potent intracellular hormone, 5α-dihydrotestosterone (DHT) (Figure 1). The quantity of this enzyme and its product, DHT, is elevated in the affected tissues of such conditions as benign prostatic hypertrophy,[1] acne, certain forms of hirsutism, and male pattern baldness.[2] Selective inhibition of this enzyme might thus provide a means of therapy for these androgen-related disorders.

In the past, control of androgen action has usually been via interference with the interaction of the androgenic hormones with their intracellular receptor.[3] This receptor, which in its free form is found in the cytosol of sensitive cells, serves to concentrate the active androgens in the cell and, after activation and transport, binds to intranuclear components to initiate the formation of mRNA and subsequent protein synthesis. Compounds such as flutamide (Figure 1), which specifically interfere with androgen–receptor interaction, thus deplete the cell of total androgen (DHT and T), although circulating levels remain the same or may even be elevated due to an interference with receptor action at the hypothalamo-pituitary axis where androgen hormone(s) regulate their own production by a negative feedback effect on the secretion of LH.[4]

Selective blockage of the conversion of T into DHT would allow T to accumulate in the androgen-sensitive cell and attenuate only those responses attributable to DHT and its metabolites. Direct action of T via the receptor as well as its metabolism to estrogen or other metabolites could proceed, thus affording a means to study the actions

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