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3,5-Dialkyl-4-(phthalimidomethyl)isoxazoles, Pyrazoles, and Isothiazoles. Novel Antiandrogens

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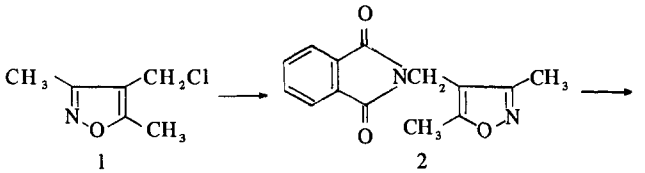
N-[(3,5-Dimethyl-4-isoxazolyl)methyl]phthalimide (**2**) was found empirically to be an effective, orally active antagonist of exogenous and endogenous androgens. Extensive modification of this molecule was undertaken tc determine whether a more active compound could be prepared. Significant activity in this class of compounds was found to be restricted to 3,5-dialkyl- (especially 3,5-dimethyl-) 4-(phthalimidomethyl)isoxazoles, pyrazoles, and isothiazoles, optionally substituted in the aromatic ring by nitro, methoxy, amino, or acetamido groups. The most active compounds in rats, both orally and subcutaneously, were *N*-[(3,5-dimethylpyrazol-4-yl)methyl]phthalimide (**42**) and its 3-amino analog **52**.

4-Chloromethyl-3,5-dimethylisoxazole[1] (**1**) is an important intermediate in a new steroid total synthesis recently reported by one of us.[2] In view of the significance of isoxazoles in medicinal chemistry, it appeared attractive to us to prepare

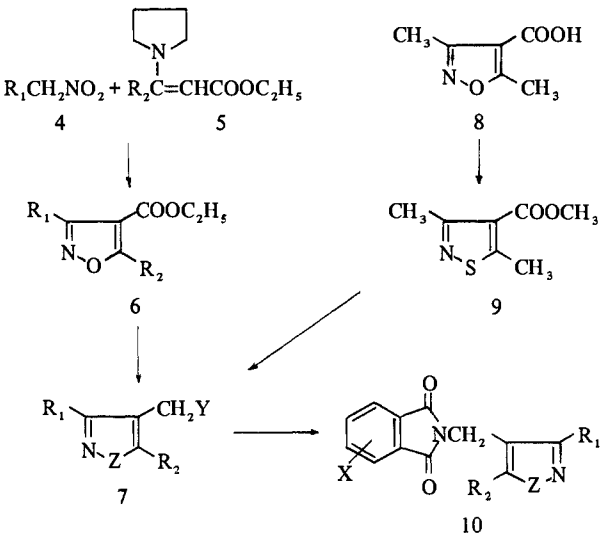


a number of derivatives of **1** containing a second nitrogen atom for biological evaluation. Among the compounds we wished to make was the amine **3**. Treatment of the chloride **1** with potassium phthalimide in DMF[3] gave, in 78% yield, the phthalimide **2** which, upon hydrazinolysis,[4] gave the desired amine. Although this compound, as its hydrochloride, did not show any useful biological activity, phthalimide **2** was found to be an effective antagonist of exogenous and endogenous androgens. The preparation and testing of this compound and various analogs constitute the subject of this report.

Chemistry. Several possibilities for chemically modifying *N*-[(3,5-dimethyl-4-isoxazolyl)methyl]phthalimide (**2**) are evident. Among the changes we have made are (a) modification of the substituents at positions 3 and 5 of the isoxazole ring, (b) substitution of the aromatic portion of the phthalimide ring, (c) conversion of the isoxazole ring to pyrazole or isothiazole, (d) changing the number of CH_2 groups between the two rings, and (e) modification of the nature of the imide ring. The compounds we have prepared are listed in Table I.

Two general synthetic routes were employed. In the first of these (Scheme I), a 4-halomethyl-3,5-dialkylisoxazole or isothiazole **7** was treated in dimethylformamide with potassium phthalimide[3] or a substituted phthalimide and K_2CO_3

Scheme I



X = H, 3- or 4-NO_2, 3- or 4-Cl, 3,4,5,6-Cl_4; Y = OH, Cl; Z = O, S; for definitions of R_1 and R_2, see Table I

at elevated temperatures.[5] With the exception of 4-bromomethylisoxazole[6] and 4-chloromethyl-5-methylisoxazole,[1] the chloromethylisoxazoles were prepared by Stork's method.[7,8] Thus, condensation of the substituted nitromethanes **4** and β-pyrrolidinoacrylates **5** in $POCl_3$-triethylamine gave the carboethoxyisoxazoles **6**, which were reduced with $LiAlH_4$.† In an early experiment carried out in ether, a violent explosion occurred during hydrolysis. We have found that if the reduction *and aqueous destruction of excess hydride* are carried out at −30° under N_2, the danger of explosion is minimized (over 100 such reductions on various

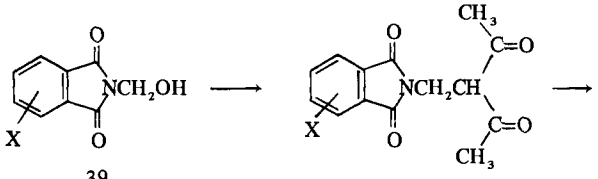
†4-Carboethoxy-3-methyl-5-(*p*-nitrophenyl)isoxazole was not stable under these reaction conditions. It was thus saponified to give the acid[9] which was reduced by the method of Ishizumi, *et al.*[10] (reaction with ethyl chloroformate followed by $NaBH_4$ reduction of the resulting carbonic–carboxylic acid anhydride).

substrates carried out without incident). The resulting hydroxymethylisoxazoles **7** (Y = OH) were treated with $SOCl_2$ in CH_2Cl_2[8] to give the 4-chloromethylisoxazoles **7** (Y = Cl). 3,5-Dimethyl-4-isoxazolecarboxylic acid (**8**), obtained by acid hydrolysis of the corresponding diethylamide,[11] was esterified[12] and then converted by the method of McGregor, *et al.*,[13] to isothiazole **9**. Reduction and treatment with $SOCl_2$ as in the isoxazole series gave 4-chloromethyl-3,5-dimethylisothiazole (**7**, $R_1 = R_2 = CH_3$; Z = S; Y = Cl). Treatment of the chloromethyl compounds **7** with potassium phthalimide, 3- and 4-nitro-,[14] 3-[15] and 4-chloro-,[16] and 3,4,5,6-tetrachlorophthalimide[17] gave compounds **2** and **11–28**. Similarly, naphthalene-2,3-[18] and -1,8-dicarboximide,‡ succinimide,‡ glutarimide,[19] and *cis*-cyclohexane-1,2-dicarboximide‡ gave the imides **29–33**.

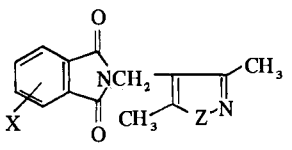
Reaction of the anion of acetylacetone with ethyl acrylate[20] or ethyl bromoacetate gave mixtures of C- and O-alkylated products in which the former predominated. Treatment of these mixtures with $H_2NOH \cdot HCl$ followed by saponification gave 3,5-dimethyl-4-isoxazolepropionic and acetic acids. Esterification[12] and subsequent treatment as for the esters **6** gave ultimately the homologous isoxazolylphthalimides **34** and **35**. Heating 4-amino-3,5-dimethylisoxazole[21] with phthalic anhydride to 200° gave phthalimide **36**. Heating phthalide and the amine **3** in a sealed tube at 230°[22] gave isoindolinone **37** in low yield. This same amine was treated with maleic anhydride followed by Ac_2O–$NaOAc$[23] to give the maleimide **38**.

The second general synthetic approach we have used (Scheme II) involves isoxazole or pyrazole ring closure as

Scheme II



39 40



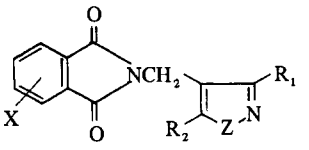
41

X = H, 3- or 4-NO_2; Z = O, NH, NCH_3, NC_6H_5

the final step. *N*-Hydroxymethylphthalimide[24] was allowed to react with acetylacetone in concentrated H_2SO_4 in a known manner[25] to give the diacetylethylphthalimide **40** (X = H). Similarly, *N*-hydroxymethyl-3- and -4-nitrophthalimide[26] were converted to **40** (X = 3- or 4-NO_2). Treatment of these materials with $H_2NOH \cdot HCl$ in acetic acid at reflux[27] gave excellent yields (>90%) of isoxazoles **41** (Z = O), thus providing alternate syntheses of compounds **2**, **21**, and **22**. In a similar manner, reaction of **40** with $H_2NNH_2 \cdot H_2O$, CH_3NHNH_2, and $C_6H_5NHNH_2$ gave pyrazoles **42–46** in over 80% yield, despite the fact that hydrazine, under different conditions, is the reagent of choice[4] for the cleavage of N-substituted phthalimides. Although this synthetic route is limited in that the isoxazole and pyrazole substituents at C-3 and C-5 must be the same, it allows the preparation of the N_1-unsubstituted pyrazolylphthalimides **42–44**, compounds which could not be obtained by a chloromethyl-type approach.

The nitro groups of compounds **16**, **21**, **22**, **27**, and **28** were reduced by $SnCl_2$ in concentrated HCl[16] to the amines **47–51**. For reasons of solubility, reduction of pyrazole derivatives **43** and **44** to **52** and **53** was more conveniently effected by catalytic hydrogenation over 5% Pd/C. The amines **48**, **49**, and **50** were acetylated with Ac_2O–pyridine in the usual manner to give amides **54–56**. Treatment of pyrazolylamines **52** and **53** with Ac_2O, propionic anhydride, and benzoyl chloride in pyridine gave intermediate diacylated materials. Selective deacylation with dilute base (K_2CO_3 in H_2O, Me_2CO, and MeOH or 0.04 *N* NaOH in MeOH) then gave the desired amides **57–61** in modest yield. The amines **48** and **49** were diazotized[28] and then warmed to give phenols **62** and **63** which, upon treatment with K_2CO_3 and Me_2SO_4, were converted to methyl ethers **64** and **65**.

Biological Results and Discussion. The compounds were tested for antiandrogenic activity in castrated rats at 4 mg/day *vs.* 20 μg/day of testosterone propionate (TP). The results, expressed as per cent inhibition of the response to TP, are presented in Table I. Examination of this data indicates that significant activity is limited to a relatively few compounds, those defined by structure **66**. Virtually any deviation from this structure results in compounds with, at best, only weak activity. It is worthy of note that the substituted pyrazoles generally have roughly equivalent sc and po activities, while the isoxazoles and isothiazoles appear to be less active orally than subcutaneously. *N*-[(3,5-Dimethyl-4-isoxazolyl)methyl]phthalimide (**2**) and *N*-[(3,5-dimethylpyrazol-4-yl)methyl]phthalimide (**42**) have been subjected to extensive secondary testing. These compounds have been shown to be nontoxic and free of androgenic, estrogenic, antigonadotropic, and antiestrogenic activities. Full details of these studies will be reported shortly.



66

X = H, 3-NH_2, 3-CH_3CONH_2, 3-NO_2, 4-OCH_3;
Z = O, S, NH, NCH_3; R_1, R_2 = CH_3, C_2H_5

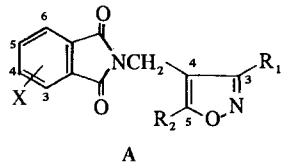
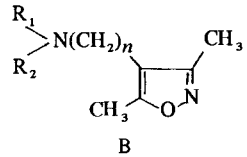
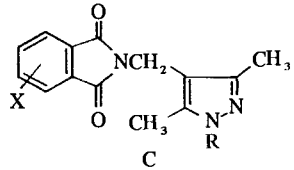
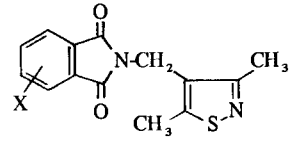
Experimental Section

The experimental procedures employed for the preparation of most of the compounds in Table I are well known and documented and thus will not be reproduced here. The physical constants for these materials are given in Table I. Melting points were determined on a Büchi capillary melting point apparatus and are uncorrected. Where analyses are indicated only by symbols of the elements, analytical results obtained for those elements were within ±0.4% of the theoretical values. Nmr, ir, uv, and mass spectra were obtained for all compounds and in each case were compatible with the assigned structure. The nmr and mass spectra, in particular, were amenable to rapid analysis. In the synthesis of many of the compounds in Table I, new intermediates were prepared. When appropriate, the structures of these materials were secured by spectral and/or microanalytical data. Full details regarding any process, intermediate, or final product not described below are available upon request.

***N*-(2,2-Diacetylethyl)-4-nitrophthalimide (40, X = 4-NO_2).** H_2SO_4 (95–97%, 250 ml) was cooled under N_2 to −10° (ice–MeOH bath) and 27.5 g (0.275 mol) of acetylacetone was added at such a rate that the temperature remained <−5° (30 min). The solution was stirred with cooling for 15 min and then 55.54 g (0.25 mol) of *N*-hydroxymethyl-4-nitrophthalimide[26] was added in one portion. The reaction mixture was stirred at 20–25° for 45 hr, poured onto

‡Aldrich Chemical Co., Inc.

Table I. Compounds Prepared for Testing as Antiandrogens. Biological Results

Compd	R_1	R_2	X	Mp, °C (solvent)	Analyses	% inhibition of response to TP[a]			
						Seminal vesicles		Ventral prostate	
						sc	po	sc	po
									
	A			B	C		D		
				A. Isoxazole Derivatives					
11	H	H	H	128–131 (CH_2Cl_2–Et_2O)	$C_{12}H_8O_3N_2$; C, H, N	24*	17	0	38***[b]
12	H	CH_3	H	122.5–125 (CH_2Cl_2–Et_2O)	$C_{13}H_{10}O_3N_2$; C, H, N	29**	34*	6	29*
13	CH_3	H	H	155.5–158 (CH_2Cl_2–Et_2O)	$C_{13}H_{10}O_3N_2$; C, H, N	27*	15	24	26*
2	CH_3	CH_3	H	125–127 (CH_2Cl_2–Et_2O)	$C_{14}H_{12}O_3N_2$; C, H, N	76***	43**	66***	45***
14	CH_3	C_2H_5	H	99–101 (Et_2O)	$C_{15}H_{14}O_3N_2$; C, H, N	14	23*	0	10
15	CH_3	C_6H_5	H	176–178 (CH_2Cl_2–Et_2O)	$C_{19}H_{14}O_3N_2$; C, H, N	0	18	1	9
16	CH_3	p-$C_6H_4NO_2$	H	219–221 (CH_2Cl_2–Et_2O)	$C_{19}H_{13}O_5N_3$; C, H, N	0	25*	23	8
47	CH_3	p-$C_6H_4NH_2$	H	188–190 (Me_2CO–hexane)	$C_{19}H_{15}O_3N_3$; C, H, N	0	0	2	10
17	C_2H_5	CH_3	H	110–112 (Et_2O)	$C_{15}H_{14}O_3N_2$; C, H, N	49***	32*	39***	40**
18	n-C_5H_{11}	CH_3	H	61–63 (Et_2O–C_5H_{12})	$C_{18}H_{20}O_3N_2$; C, H, N	0	5	0	0
19	C_6H_5	CH_3	H	182–184 (CH_2Cl_2–Et_2O)	$C_{19}H_{14}O_3N_2$; C, H, N	15	8	19	5
20	C_6H_5	C_6H_5	H	189–191 (CH_2Cl_2–Et_2O)	$C_{24}H_{16}O_3N_2$; C, H, N	10	9	0	16
21	CH_3	CH_3	3-NO_2	175–178.5 (Me_2CO–hexane)	$C_{14}H_{11}O_5N_3$; C, H, N	32*	26	32**	37**
22	CH_3	CH_3	4-NO_2	165.5–167 (Me_2CO–hexane)	$C_{14}H_{11}O_5N_3$; C, H, N	20	24	17	39**
48	CH_3	CH_3	3-NH_2	183.5–185.5 (Me_2CO–hexane)	$C_{14}H_{13}O_3N_3$; C, H, N	79***	49**	78***	53***
49	CH_3	CH_3	4-NH_2	221–223 (Me_2CO–hexane)	$C_{14}H_{13}O_3N_3$; C, H, N	42**	37*	39***	40***
54	CH_3	CH_3	3-CH_3CONH	181–182.5 (CH_2Cl_2–Et_2O)	$C_{16}H_{15}O_4N_3$; C, H, N	0	41***	9	26
55	CH_3	CH_3	4-CH_3CONH	212.5–214.5 ($CHCl_3$)	$C_{16}H_{15}O_4N_3$; C, H, N	3	29**	19	12
23	CH_3	CH_3	3-Cl	140–143 (CH_2Cl_2–Et_2O)	$C_{14}H_{11}O_3N_2Cl$; C, H, N, Cl	19	10	27*	5
24	CH_3	CH_3	4-Cl	140.5–143 (CH_2Cl_2–Et_2O)	$C_{14}H_{11}O_3N_2Cl$; C, H, N, Cl	31	16	41**	10
62	CH_3	CH_3	3-OH	193–194.5 (Me_2CO)	$C_{14}H_{12}O_4N_2$; C, H, N	13	0	38**	3
63	CH_3	CH_3	4-OH	228–231.5 (Me_2CO)	$C_{14}H_{12}O_4N_2$; C, H, N	26***	0	34**	3
64	CH_3	CH_3	3-OCH_3	194–198 (CH_2Cl_2–Et_2O)	$C_{15}H_{14}O_4N_2$; C, H, N	7	0	0	0
65	CH_3	CH_3	4-OCH_3	170–172 (CH_2Cl_2–Et_2O)	$C_{15}H_{14}O_4N_2$; C, H, N	39***	10	38***	23
25	CH_3	CH_3	3,4,5,6-Cl_4	248–250 (C_6H_6)	$C_{14}H_8O_3N_2Cl_4$; C, H, N, Cl	0	13	0	9
				B. Modified Imides					
	Imide (R_1R_2)	n							
34	Phthalimide	3		97.5–100 (CH_2Cl_2–Et_2O)	$C_{16}H_{16}O_3N_2$; C, H, N	0	27*	0	4
35	Phthalimide	2		138.5–142.5 (CH_2Cl_2–Et_2O)	$C_{15}H_{14}O_3N_2$; C, H, N	9	1	5	23*
36	Phthalimide	0		172–174 (Me_2CO)	$C_{13}H_{10}O_3N_2$; C, H, N	24*	13	15	34**
29	Napthalene-2,3-dicarboximide	1		245–246 ($CHCl_3$–Me_2CO)	$C_{18}H_{14}O_3N_2$; C, H, N	0	12	0	2
30	Napthalene-1,8-dicarboximide	1		238.5–242.5 (Me_2CO)	$C_{18}H_{14}O_3N_2$; C, H, N	0	28**	6	13
31	Succinimide	1		119.5–122 (CH_2Cl_2–Et_2O)	$C_{10}H_{12}O_3N_2$; C, H, N	10	0	9	0
32	Glutarimide	1		71.5–74 (i-Pr_2O)	$C_{11}H_{14}O_3N_2$; C, H, N	11	16	0	12
38	Maleimide	1		117–120 (CH_2Cl_2–Et_2O)	$C_{10}H_{10}O_3N_2$; C, H, N	33	38*	23	79***[c]
33	*cis*-Cyclohexane-1,2-dicarboximide	1		102–104.5 (CH_2Cl_2–Et_2O)	$C_{14}H_{18}O_3N_2$; C, H, N	21	17	5	38***
37	Isoindolinone	1		92.5–95 (CH_2Cl_2–Et_2O)	$C_{14}H_{14}O_2N_2$; C, H, N	22	32*	13	56***

C. Pyrazole Derivatives

	R	X					
42	H	H	196–198 (Me_2CO)	$C_{14}H_{13}O_2N_3$; C, H, N	65***	72***	56**	80***
43	H	3-NO_2	233–234 (Me_2CO)	$C_{14}H_{12}O_4N_4$; C, H, N	25**	20	31**	35**
44	H	4-NO_2	226.5–228 (Me_2CO)	$C_{14}H_{12}O_4N_4$; C, H, N	21	13	5	8
52	H	3-NH_2	211–213 (Me_2CO)	$C_{14}H_{14}O_2N_4$; C, H, N	62***	58***	65***	67***
53	H	4-NH_2	226–228 (Me_2CO)	$C_{14}H_{14}O_2N_4$[d]	0	30**	12	30*
57	H	3-CH_3CONH	239.5–241 (Me_2CO)	$C_{16}H_{16}O_3N_4$; C, H, N	40**	74***	37**	82***
58	H	4-CH_3CONH	262–269 dec (Me_2CO)	$C_{16}H_{16}O_3N_4$; C, H, N	0	38**	2	49***
59	H	3-C_2H_5CONH	184–186 (Me_2CO)	$C_{17}H_{18}O_3N_4$; C, H, N	38**	64***	50***	60***
60	H	4-C_2H_5CONH	225–229 (Me_2CO)	$C_{17}H_{18}O_3N_4$; C, H, N	6	6	6	23
61	H	4-C_6H_5CONH	249.5–252 (CH_3CN)	$C_{21}H_{18}O_3N_4$; C, H, N	0	24*	6	28
45	CH_3	H	139.5–142 (CH_2Cl_2–Et_2O)	$C_{15}H_{15}O_2N_3$; C, H, N	43***	40***	40***	47***
46	C_6H_5	H	143.5–146.5 (Me_2CO–hexane)	$C_{20}H_{17}O_2N_3$; C, H, N	0	7	0	17

D. Isothiazole Derivatives

	X						
26	H	158–160 (CH_2Cl_2–Et_2O)	$C_{14}H_{12}O_2N_2S$; C, H, N, S	75***	33**	62**	43***[c]
27	3-NO_2	176.5–178 (CH_2Cl_2–Et_2O)	$C_{14}H_{11}O_4N_3S$; C, H, N, S	26*	1	14	11
28	4-NO_2	159–161 (CH_2Cl_2–Et_2O)	$C_{14}H_{11}O_4N_3S$; C, H, N, S	11	3	3	24
50	3-NH_2	186–187.5 (Me_2CO–hexane)	$C_{14}H_{13}O_2N_3S$; C, H, N, S	71***	29**	61***	35**
51	4-NH_2	247.5–248 (Me_2CO–hexane)	$C_{14}H_{13}O_2N_3S$; C, H, N, S	10	8	3	16
56	3-CH_3CONH	205.5–206.5 (CH_2Cl_2–ether)	$C_{16}H_{15}O_3N_3S$; C, H, N, S	0	10	0	26*

[a] Compounds were tested at 4 mg/rat/day *vs.* testosterone propionate (TP, 20 μg sc/rat/day). For details see text and Experimental Section. [b] *, $p < 0.05$, **, $p < 0.01$, ***, $p < 0.001$ *vs.* testosterone propionate alone group. [c] Toxic. [d] Despite micronization and drying for extended periods at 80° (0.01 mm), this material contained *ca.* 0.1 mol of acetone, as shown by nmr. Analysis for $C_{14}H_{14}O_2N_4 \cdot 0.1C_3H_6O$ (C, H, N) was satisfactory. The molecular weight of 270 was confirmed by the mass spectrum.

ice, and filtered. The solid was washed with H_2O, sucked dry, triturated with 1 l. of hot EtOH and 150 ml of H_2O, cooled, filtered, and crystallized twice from 2:1 Me_2CO–H_2O to give analytically pure product as 41.5 g (55%) of white needles: mp 135–139°; uv max (EtOH) 205 nm (ε 19,250) and 276 (9400); ir ($CHCl_3$) 1782 and 1727 (imide and enolized β-diketone) and 1548 and 1341 cm^{-1} ($-NO_2$); nmr (2:1 $CDCl_3$–DMSO-d_6) δ 2.38 (s, 6, $2CH_3CO$), 4.78 (s, 2, CH_2), 8.42 (m, 3, C_6H_3), and 17.5 ppm (s, 1, OH) (the compound is entirely in the enolic form in solution); mass spectrum (70 eV) *m/e* 262 ($M^+ - C_2H_2O$), 192, 103, 75, and 43 (base peak). *Anal.* C, H, N.

***N*-[(3,5-Dimethylpyrazol-4-yl)methyl]-4-nitrophthalimide (44).** To a mixture of 30.4 g (0.10 mol) of **40** (X = 4-NO_2) and 160 ml of AcOH was added 5.34 ml (5.5 g, 0.11 mol) of $H_2NNH_2 \cdot H_2O$. The resulting mixture was heated at reflux under N_2 for 3.0 hr, cooled, diluted with $CHCl_3$, washed with excess 3 *N* NaOH and H_2O, and dried (Na_2SO_4). Two crystallizations of the crude product from Me_2CO gave the pyrazole **44** as 15.22 g (51%) of small, light yellow plates: mp 226.5–228°; uv max (EtOH) 208 nm (ε 28,600) and 238 (20,250); ir (KBr) 3190 (NH), 1780 and 1714 (imide), 1624 and 1584 (aromatic), and 1541 and 1345 cm^{-1} (nitro); nmr ($CDCl_3$) δ 2.20 (s, 6, 2 pyrazole-CH_3), 4.53 (s, 2, pyrazole-CH_2), 8.08 (m, 1) and 8.60 (m, 2, C_6H_3), and 10.6 ppm (s, 1, NH); mass spectrum (70 eV) *m/e* 300 (M^+) and 108 (base peak). *Anal.* C, H, N.

4-Amino-*N*-[(3,5-dimethylpyrazol-4-yl)methyl]phthalimide (53). A suspension of 40.0 g (0.133 mol) of nitro compound **44** and 4.0 g of 5% Pd/C catalyst in 2.0 l. of MeOH was hydrogenated at atmospheric pressure. After the uptake of H_2 (8.2 l.) had ceased (5.0 hr). the suspension was diluted to *ca.* 6 l. with MeOH, heated to bring the amine into solution, and filtered. The crude product was crystallized twice from acetone to give, after micronization and drying at 80° (0.01 mm) for 18 hr, 13.52 g (50%) of yellow powder containing *ca.* 0.1 mol of acetone: mp 226–228°; uv max (EtOH) 250 nm (sh, ε 19,700), 259 (21,350), 306 (4750), and 378 (4000); ir (KBr) 3478, 3386, and 3240 (NH_2 and NH), 1765 and 1706 (imide), 1600 and 1502 (aromatic), and 1621 cm^{-1} (NH_2); nmr (DMSO-d_6) δ 2.12 (s, Me_2CO), 2.27 (s, 6, 2 pyrazole-CH_3), 4.47 (s, 2, pyrazole-CH_2), 6.48 (s, 2, NH_2), 6.9 (m, 2) and 7.53 (d, 1, C_6H_3), and 12.15 ppm (s, 1, NH); mass spectrum (70 eV) *m/e* 270 (M^+), 175, 109, and 108 (base peak). *Anal.* ($C_{14}H_{14}O_2N_4 \cdot 0.1C_3H_6O$) C, H, N.

4-Acetamido-*N*-[(3,5-dimethylpyrazol-4-yl)methyl]phthalimide (58). A solution of 13.51 g (0.050 mol) of the 4-aminophthalimide **53** and 18.9 ml (20.4 g, 0.20 mol) of Ac_2O in 125 ml of pyridine was heated at 100° under N_2 for 16 hr. Work-up ($CHCl_3$) in the normal manner gave 20 g of gummy, tan solid. To a suspension of 16 g of this diacylated product in 200 ml of MeOH was added 8.0 ml of 1 *N* NaOH. The mixture was stirred at 20° for 10 min, quickly cooled in an ice bath, and filtered. The solid was washed with cold MeOH and Et_2O and crystallized from Me_2CO to give 6.85 g (55%) of white, powdery solid of mp 262–269° dec. A second crystallization of this material from acetone gave the analytical sample: mp 261–268° dec; uv max (EtOH) 241 nm (ε 29,600), 252 (28,500), 261 (sh, 23,700), and 328 (3700); ir (KBr) 3270, 3226, and 3160 (2NH), 1760 and 1727 (imide), 1720 (amide), 1650 and 1490 (aromatic), and 1568 cm^{-1} (amide II); nmr (DMSO-d_6) δ 2.16 (s, 3, CH_3CONH), 2.25 (s, 6, 2 pyrazole-CH_3), 4.49 (s, 2, pyrazole-CH_2), 7.82 (m, 2) and 8.17 (m, 1, C_6H_3), and 13.0 (s, 1) and 16.2 ppm (s, 1, 2NH); mass spectrum (70 eV) *m/e* 312 (M^+) and 108 (base peak). *Anal.* C, H, N.

Biological Method. Charles River rats were castrated at 21–22 days of age and were treated for 7 consecutive days beginning 7 days post castration. Compounds (4 mg/rat/day) were dissolved or suspended in sesame oil and administered in a volume of 0.2 ml/rat/day either orally or subcutaneously. Testosterone propionate (TP) was administered concurrently by separate subcutaneous injection at a different body site at a dosage of 20 μg/0.2 ml/rat/day in sesame oil. Each treatment group consisted of 7–8 rats. All rats were autopsied on the day after the last treatment day and the weights of the seminal vesicles and ventral prostates were determined. Per cent inhibition of the response to TP (Table I) was computed by the following formula

$$\frac{(\text{TP alone}) - (\text{TP} + \text{compound})}{(\text{TP alone}) - (\text{controls})} \times 100$$

Statistical differences were calculated by t test.

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Selectivity in New β-Adrenergic Blocking Agents. (3-Amino-2-hydroxypropoxy)benzamides

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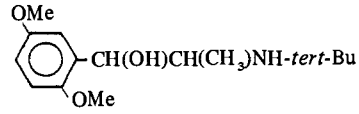
The β-adrenergic receptor blocking properties of new open-chain and lactam-type benzamido analogs of practolol (**2**) were investigated. These compounds display a competitive blocking activity on both vascular and myocardial β receptors. However, subtle structural changes in the aromatic moiety profoundly affected their organ specificity toward each of these receptors. Since all of the test compounds including practolol (**2**) share similar lipohydrophilic character, it may be concluded that their ability to selectively block either myocardial or vascular receptors depends primarily on electronic and steric factors.

It has been recently suggested that adrenergic β receptors may be classified into β-1 (*e.g.*, myocardial) and β-2 (*e.g.*, vascular) receptor subtypes.[1,2] The basis for this classification is the observed differences in sensitivity of adrenergic β receptors in various organs to β stimulants and the selective action of some β-adrenergic receptor blockers. With regard to selectivity, it appears that there exists at least three categories of β-receptor antagonists:[3] a group that selectively blocks vascular β receptors, represented by butoxamine (**1**); one that selectively blocks cardiac β receptors, represented by practolol (**2**); and one that blocks β receptors in all tissues ("nonselective" β blockers), represented by propranolol (**3**). Structure–activity relationships of numerous agonists and antagonists for the adrenergic β receptors have been extensively reviewed.[4-8] However, the organ specificity displayed by various β blockers is as yet poorly understood. In order to study in detail the possible implications of chemical structure on selectivity in β blockade, practolol (**2**) was chosen as a reference compound. This is because of the recognized importance of cardioselective β blockers in clinical practice. The present report is concerned with the syntheses and adrenergic β-blocking activity in the cardiovascular system of a series of benzamido analogs of practolol (**2**).



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Chemistry. The open-chain (Table I, compounds **15–17**) and lactam-type (Table I, compounds **18** and **19**) benzamido analogs of practolol (**2**) were prepared in two steps: (a) reaction of epichlorohydrin with the corresponding substituted phenols, in the presence of a base, and (b) treatment of the resulting 1-aryloxy-2,3-epoxypropanes (Table II, compounds **9–14**) with the appropriate amine to give the desired (±)-1-amino-3-aryloxypropan-2-ols (Table I, compounds **15–19**). The starting materials for compounds **10–12**, namely, 4-hydroxybenzamide, 3-hydroxybenzamide, and 3,5-dihydroxybenzamide (α-resorcylamide), respectively, were prepared in high yield by aminolysis of the corresponding esters in aqueous ammonia at room temperature. The phenolic lactams, 2,3,4,5-tetrahydro-7-hydroxy-1*H*-2-benzazepin-1-one[9] (**7**) and 2,3-dihydro-8-hydroxy-1,4-benzoxazepin-5(4*H*)-one (**8**) (the starting materials for compounds **13** and

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