Berbanes: A New Class of Selective α_2-Adrenoceptor Antagonists

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The α-adrenoceptor blocking properties of some berbanes have been studied and compared with those of idazoxan, yohimbine, phentolamine, and prazosin. Their effects on presynaptic α_2-adrenoceptors were studied on chemical neurotransmission of isolated rat vas deferens and longitudinal muscle strip of guinea pig ileum; xylazine or norepinephrine was employed as agonist. The α_1-adrenoceptor blocking activities of the berbanes were tested on isolated rat vas deferens and rabbit pulmonary artery by using phenylephrine or norepinephrine as agonist. The antagonistic activity of the berbanes and the reference compounds on α_2- and α_1-adrenoceptors was characterized by the apparent pA_2 values. Of the compounds studied, [8a*S**-(8aα,12aα,13aα)]-11α-hydroxy-5,6,8a,9,10,11,12,12a,13,13a-decahydro-8*H*-benzo[*g*]-1,3-benzodioxolo[5,6-*a*]quinolizine, **6d**, proved to be the most selective antagonist at the presynaptic α_2-adrenoceptors (α_1:α_2 ratio = 1659). Since blockade of α_2-adrenoceptors located on noradrenergic axon terminals leads to an increase of norepinephrine release, this compound could have potential as an antidepressant agent.

There is now considerable evidence that there are at least two distinct subclasses of α-adrenoceptors: α_1- and α_2-adrenoceptors.[1-4] This pharmacological classification is independent of anatomical arrangement.[5] α_2-Adrenoceptors can be differentiated from α_1-adrenoceptors by the specificity of a series of agonists and antagonists acting on these receptors. Such a subclassification of α-adrenoceptors opens possibilities for the development of new drugs with a high selectivity for each receptor subtype.

Several structures have been reported that show significant selectivity as antagonists at α_1 (e.g., prazosin) or α_2-adrenoceptors (e.g., benzodioxans,[6,7,9] benzoquinolizines,[8,10] pyridinylpiperazines,[11] benzazepines,[12] benzofuroquinolizines[12a]). Combination of 1,4-benzodioxan and imidazoline moieties[1,13] led to the discovery of idazoxan (RX 781094, 2-(1,4-benzodioxan-2-yl)-2-imidazoline), which possesses significant α_2-adrenoceptor selectivity. Convincing experimental evidence is available that norepinephrine (NE), via stimulation of α_2-adrenoceptors located at the varicose axon terminals of noradrenergic neurons, controls the further release of NE.[14-17] Recently, it has been suggested that a common underlying mechanism for the action of antidepressants may be the ability to alter α_2-adrenoceptor sensitivity,[18,19] thus increasing NE release.[19] In addition, the α_2-adrenoceptors on noradrenergic neurons in the cerebral cortex are thought to be supersensitive, which would tend to reduce the release of NE. Therefore, it can be suggested that treatment with a compound that acts as an antagonist at presynaptic α_2-adrenoceptors could provide an effective and novel treatment for depression. We report here the synthesis and pharmacological testing of new berbane derivatives, which can be regarded as depyrrolo analogues of the biologically potent yohimbine and reserpine alkaloids.[20-25] The berbanes may therefore possess similar α-adrenoceptor activity.

Chemistry

Preparation of the berbane skeleton[21] has been reported earlier.[22-27] The tetracyclic ketones **2–4** were synthesized from **1**[22,25-27] (Schemes I and II). The derivatives **2**, **3**, and **4** were reduced with $NaBH_4$, yielding alcohols **5**, **6**, and **7**, respectively.

The stereochemistry of the alcohols has been verified by IR and NMR spectroscopy (Tables I–III).

The intensive Bohlmann-band system in the IR spectra

Scheme I

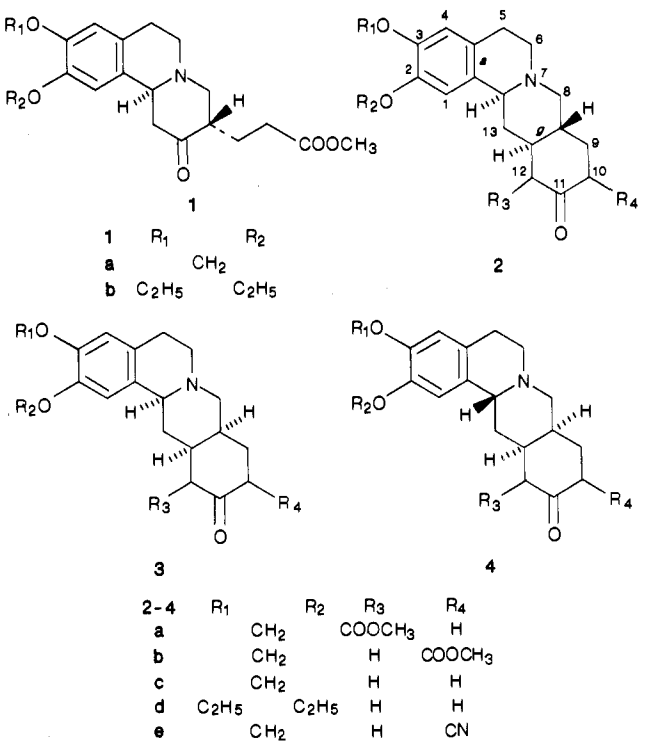

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Table I. Chemical and IR Data

starting compd	product	yield, %	mp, °C	formula	IR, cm^{-1} OH	Bohlmann bands	
3a	**6a**	71	159.5–162	$C_{20}H_{25}NO_5$	3500	2750–2800	1700[c]
3b	**6b**	69	148–150	$C_{20}H_{25}NO_5$	3460	2750–2800	1700[c]
3c	**6c**[a]	59.8	173–175	$C_{18}H_{23}NO_3$	3460	2750–2800	
	6d[a]	16.2	214–217	$C_{18}H_{23}NO_3$	3450	2750–2850	
2a	**5a**	58	166	$C_{20}H_{25}NO_5$	3480	2750–2850	1720[c]
2b	**5f**[a]	21	185–187	$C_{20}H_{25}NO_5$	3350	2750–2800	1710[c]
	5b[a]	38	205	$C_{20}H_{25}NO_5$	3400	2750–2800	1700[c]
2c	**5c**	60	217–219	$C_{18}H_{23}NO_3$	3350	2750–2800	
4a	**7e**[a]	37	202–203	$C_{20}H_{25}NO_5$	3450	2750–2800	1730[c]
4c	**7c**[a]	49	212–216[b]	$C_{18}H_{24}NO_3Cl$	3350	2750–2850	
3d	**6g**	61	135–139	$C_{21}H_{31}NO_3$	3390	2750–2800	
3e	**6k**	87	225–226	$C_{19}H_{22}N_2O_3$	3450	2700–2750	2230[e]
6l	**6m**	90	165–167	$C_{21}H_{29}NO_4$		2750–2850	1705[f]
6c	**6n**	92	153	$C_{20}H_{25}NO_4$		2750–2850	1720[f]
6d	**6o**	89	155	$C_{20}H_{25}NO_4$		2750–2850	1720[f]
3a	**6h**	47	243–245[b]	$C_{19}H_{26}NO_4Cl$	3350	2750–2800	
3b	**6i**	41.5	152–155	$C_{19}H_{25}NO_4$	3400	2750–2850	
2a	**5h**	42	245–250[b]	$C_{19}H_{26}NO_4Cl$	3400	2750–2850	
6c	**6j**	47	202[g]	$C_{17}H_{24}NO_3Br$	3400	2750–2800	
6a	**6p**	59	142–146	$C_{21}H_{27}NO_5$	3480	2750–2800	1710[d]

[a] Separation by flash chromatography. [b] HCl salt. [c] CO_2CH_3. [d] $CO_2C_2H_5$. [e] CN. [f] AcO. [g] HBr salt.

Table II. ^1H NMR Data[a]

compd	1 H, s C-6 H	1 H, s C-9 H	2 H, s OCH_2O	1 H, m C-11 H	half-width, Hz	3 H, s $COOCH_3$	3 H, s AcO
6a	6.50	6.62	5.85	4.25 eq	5	3.82	
6b	6.50	6.72	5.84	4.25 eq	6	3.68	
6c	6.50	6.72	5.85	4.05 eq	10		
6d	6.50	6.70	5.85	3.75 ax	30		
5a	6.55	6.65	5.85	3.80 ax	20		
5f	6.50	6.70	5.84	4.35 eq	6	3.70	
5b	6.52	6.70	5.85	3.85 ax	24	3.71	
5c	6.55	6.75	5.85	3.65 ax	30		
7e	6.55	6.60	5.85	4.20 eq	11	3.80	
7c	6.50	6.65	5.85	3.75 ax	30		
6g	6.60	6.70		4.25 eq	8		
6k	6.50	6.72	5.85	4.20 eq	8		
6m	6.55	6.64		4.98 eq	10		1.92
6n	6.53	6.69	5.86	5.03 eq	10		1.90
6o	6.52	6.66	5.84	4.86 ax	30		1.96

[a] δ ($CDCl_3$).

of all these compounds supports the trans quinolizidine structure.[28a]

Table III. ^{13}C NMR Data of **6a–c**[a]

	6a	**6b**	**6c**
C-1	105.02	105.37	105.29
C-2	145.72*	145.84*	145.88*
C-3	145.55*	145.56*	145.62*
C-4	108.35	108.27	108.29
C-4a	128.08	127.80	127.79
C-5	29.89	29.87	29.53
C-6	52.59	52.75	52.84
C-8	62.32	62.29	62.48
C-8a	37.11$^+$	36.70	36.47
C-9	20.48	24.09	20.83
C-10	31.66″	47.19	33.00
C-11	65.57	65.87	66.32
C-12	49.69	36.46	37.28
C-12a	37.40$^+$	33.86	34.44
C-13	31.25″	34.86	34.95
C-13a	63.96	64.26	64.29
C-13b	131.40	131.72	131.79
$COOCH_3$	51.83	51.75	
OCH_2O	100.57	100.56	100.56
$COOCH_3$	175.69	176.24	

[a] δ ($CDCl_3$). Assignments of signals (*), ($^+$), or (″) may be interchanged.

Generally it has been observed[28b] that the chemical shift data and the coupling constants of the carbinol proton

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(21) Normal berbane, [8a*R**-(8aβ,12aα,13aα)]-5,6,8a,9,10,11,12,12a,13,13a-decahydro-8*H*-dibenzo[*a*,*g*]-quinolizine; alloberbane, [8a*S**-(8aα,12aα,13aα)]-5,6,8a,9,10,11,12,12a,13,13a-decahydro-8*H*-dibenzo[*a*,*g*]-quinolizine; epialloberbane, [8a*S**-(8aα,12aα,13aβ)]-5,6,8a,9,10,11,12,12a,13,13a-decahydro-8*H*-dibenzo[*a*,*g*]-quinolizine.

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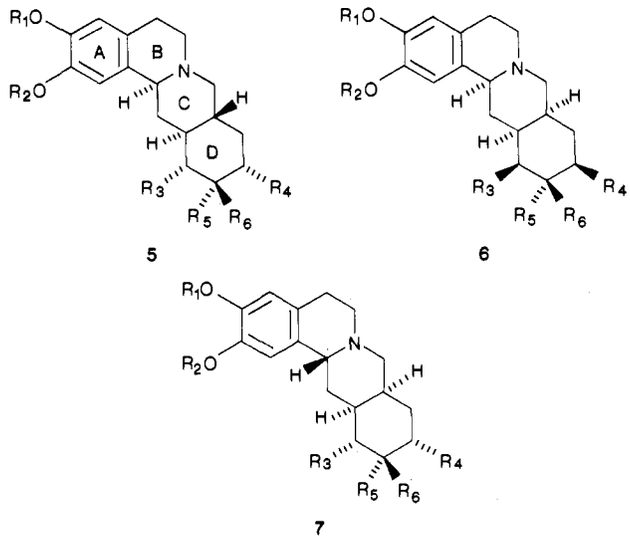
Scheme II



5 6

7

5-7	R_1	R_2	R_3	R_4	R_5	R_6
a		CH_2	$COOCH_3$	H	H	OH
b		CH_2	H	$COOCH_3$	H	OH
c		CH_2	H	H	H	OH
d		CH_2	H	H	OH	H
e		CH_2	$COOCH_3$	H	OH	H
f		CH_2	H	$COOCH_3$	OH	H
g	C_2H_5	C_2H_5	H	H	H	OH
h		CH_2	CH_2OH	H	H	OH
i		CH_2	H	CH_2OH	H	OH
j	H	H	H	H	H	OH
k		CH_2	H	CN	H	OH
l	CH_3	CH_3	H	H	H	OH
m	CH_3	CH_3	H	H	H	$OCOCH_3$
n		CH_2	H	H	H	$OCOCH_3$
o		CH_2	H	H	$OCOCH_3$	H
p		CH_2	$COOC_2H_5$	H	H	OH

reflect the steric position of the OH group. The signals at higher chemical shift values (4.05–4.35 ppm) possessing smaller half-widths (5–10 Hz) are characteristic of equatorial protons (axial OH group), while the signals of axial protons appear at lower values (3.65–3.85 ppm) with wider half-widths (20–30 Hz). The steric position of C-10 and C-12 substituents in most cases can also be deduced from the coupling constants $J_{10,11}$ and $J_{11,12}$ or half-width of C-11 H.[28c,d]

Reduction of **3a–e** yielded alcohols **6a–c,g,k**, respectively, as the main products. The proton NMR data indicate the β-axial position for the C-11 OH. The equatorial orientation of the C-10 and C-12 COOMe groups (compounds **6b** and **6a**, respectively) follows from the ^{13}C NMR data (see Table III). An axial COOMe substituent in either the C-10 or the C-12 position would exert a shielding–gauche effect on carbon C-8a in comparison with the respective value of **6c** (**6c**, 36.47 ppm; **6b**, 36.70 ppm; **6a**, 37.11 ppm).

Upon reduction of **3c**, **6d** was isolated as the minor product; the ^1H NMR spectrum indicates an α-equatorial OH group.

The major product of reduction of ketone **2c** was **5c**, having a C-11 β-equatorial hydroxyl group. Similarly, reduction of keto esters **2a** and **2b** gave rise to alcohols **5a** and **5b** with C-11 β-equatorial hydroxyl groups and α-equatorial CO_2Me groups. Upon reduction of keto ester **2b**, in addition to alcohol **5b** as the main product, a minor product **5f** was separated by flash chromatography. Alcohol **5f**, as expected, contains the C-11 OH group in an α-axial position.

Reduction of compounds **4a** and **4c** gave different stereochemical results. Reduction of the keto ester **4a** produced alcohol **7e** as the major product, containing the C-11 OH in an α-axial position. Ketone **4c** gave alcohol **7c** with the C-11 β-equatorial hydroxyl group.

In order to prepare dialcohols **6h,i** and **5h** for pharmacological studies, ketones **3a,b** and **2a** were reduced with a large excess of $NaBH_4$. For the same purpose, alcohols **6l**,[26] **6c**, and **6d** were acetylated to give **6m** and **6n** with a β-axial and **6o** with an α-equatorial acetoxy group. Conversion of methyl ester **6a** to the corresponding ethyl ester **6p** was carried out in the presence of $4\text{-}MeC_6H_4SO_3H$ catalyst in boiling EtOH. BBr_3 dealkylation of **6c** gave **6j**.

Biological Results and Discussion

Antagonist activities of these compounds on presynaptic (α_2) and postsynaptic (α_1) adrenoceptors were determined in the rat isolated field stimulated vas deferens.[29] In this preparation, presynaptic α_2-adrenoceptor agonists such as xylazine characteristically inhibit stimulation-evoked contractions with an ED_{50} of 8×10^{-8} M. Phenylephrine, a relatively pure α_1-adrenoceptor agonist, produced dose-dependent contractions. These pre- and postsynaptic effects were preferentially blocked by selective inhibitors of α_1- and α_2-adrenoceptors. Quantitative analysis of the antagonism of both selective agonists by the compounds studied resulted in a calculation of the ratio of $pA_2(\alpha_1)$: $pA_2(\alpha_2)$ as a measure of the selectivity for either α-adrenoceptor site. Of the reference drugs reported in Table IV, idazoxan was the most potent and selective α_2-antagonist in the rat vas deferens, while yohimbine was found to be less potent and selective. However, several members of the berbane series (Table IV) showed a highly selective α_2-adrenoceptor antagonist activity, with very low potency on postsynaptic α_1-adrenoceptors in the vas deferens. There was a significant difference between the alloberbane (**6**) and epialloberbane (**7**) skeletons as far as their potency on α_2-adrenoceptors is concerned: alloberbanes proved to be about 10 times more potent. Of the compounds tested, [8aS*-(8aα,12aα,13aα)]-11α-hydroxy-5,6,8a,9,10,11,12,-12a,13,13a-decahydro-8*H*-benzo[*g*]-1,3-benzodioxolo[5,6-*a*]quinolizine (**6d**) proved to be the most selective α_2-adrenoceptor antagonist. Compound **6c** also proved to be very active as an α_2-adrenoceptor antagonist (α_1:α_2 ratio = 602). The selectivity ratios for **6d**, idazoxan, yohimbine, and phentolamine were 1659, 117.5, 4.7, and 0.57, respectively. Prazosin possessed by far the highest affinity for the postsynaptic α_1-adrenoceptors which were previously stimulated with phenylephrine, followed in decreasing order of potency by prazosin > phentolamine > yohimbine > idazoxan > **6d**, respectively.

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Table IV. Presynaptic α_2-Adrenoceptor and Postsynaptic α_1-Adrenoceptor pA_2 Values in Rat Vas Deferens and Presynaptic α_2-Adrenoceptor pA_2 Values in the Longitudinal Muscle Strip of Guinea Pig Ileum

	vas deferens[a] $pA_2 \pm$ SD			long. muscle strip $pA_2 \pm$ SD[e]	
compd	α_2-adrenoceptor[b]	α_1-adrenoceptor[c]	selectivity:[d] α_1:α_2 ratio	xylazine	*l*-NE
5a	7.41 ± 0.10	4.86 ± 0.83	354.8	6.40 ± 0.51	6.17 ± 0.81
5b	5.64 ± 0.30	5.98 ± 0.98	0.46	4.82 ± 0.44	6.55 ± 0.88
5c	7.12 ± 0.02	5.02 ± 0.12	125.9	7.02 ± 0.13	5.95 ± 0.37
5h	6.21 ± 0.11	5.25 ± 0.30	9.1	6.72 ± 0.89	6.31 ± 0.81
6a	7.18 ± 0.36	6.18 ± 0.44	10	7.86 ± 0.19	7.80 ± 0.46
6b	5.80 ± 0.16	4.80 ± 0.22	10	6.61 ± 0.29	7.82 ± 0.15
6c	7.63 ± 0.44	4.85 ± 0.15	602	0.13 ± 0.08	7.62 ± 0.34
6d	8.17 ± 0.01	4.95 ± 0.11	1659	8.07 ± 0.20	8.26 ± 0.46
6g	6.41 ± 0.08	<4	>257		
6h	5.60 ± 0.63			6.32 ± 0.22	6.69 ± 0.13
6i	5.91 ± 0.20	<4	>81.2	6.51 ± 0.41	6.30 ± 0.31
6j	5.74 ± 0.11	<4	>54.9		
6k	6.10 ± 0.07	<4	>125.8		6.67 ± 0.78
6l	6.31 ± 0.22	<4	>204.1		<4
6m	6.61 ± 0.06	4.54 ± 0.61	117.0		6.19 ± 0.23
6n	7.30 ± 0.15	4.55 ± 0.39	562.3		8.21 ± 0.84
6p	7.39 ± 0.11	5.51 ± 0.57	263	7.44 ± 0.28	6.77 ± 0.22
7c	6.77 ± 0.06	5.66 ± 0.11	12.8		6.90 ± 0.08
7e	6.21 ± 0.19	5.66 ± 0.32	3.5		
yohimbine	7.72 ± 0.11	7.05 ± 0.19	4.7	7.36 ± 0.17	7.59 ± 0.41
idazoxan	8.07 ± 0.04	6.00 ± 0.16	117.5	7.41 ± 0.18	7.49 ± 0.08
phentolamine	7.78 ± 0.05	8.02 ± 0.25	0.57	7.81 ± 0.12	8.82 ± 0.22
prazosin	6.84 ± 0.25	9.36 ± 0.11	0.003	<5	<5

[a] Determined by using isolated rat vas deferens; pA_2 values were calculated according to Arunlakshana and Schild.[30] [b] Antagonism of the α_2-adrenoceptor agonist xylazine (0.1-Hz stimulation). [c] Antagonism of the α_1-adrenoceptor agonist (−)-phenylephrine. It should be noted that the maximal dose ratios reached by the antagonists studied (compounds **5–7**) were not higher than 8. This indicates poor affinity of the berbanes tested on α_1-receptors. [d] Ratio of antilogs of $pA_2(\alpha_1)/pA_2(\alpha_2)$. [e] Longitudinal muscle strip of guinea pig ileum, 0.1-Hz field stimulation; pA_2 values were calculated as described by Arunlakshana and Schild.[30]

Table V. Effect of α_2-Adrenoceptor Antagonists on Postsynaptic α_1-Adrenoceptors of Rabbit Pulmonary Artery

compd	$pA_2 \pm$ SD[a]	relative potency[b]
5a	4.81 ± 0.27	0.01
6a	6.19 ± 0.07	0.22
6c	4.98 ± 0.92	0.01
6d	5.39 ± 0.33	0.03
yohimbine	6.83 ± 0.01	1
idazoxan	6.85 ± 0.21	1.1
phentolamine	7.82 ± 0.08	9.8
prazosin	8.76 ± 0.02	85.0

[a] *l*-Norepinephrine was used as agonist ($pD_2 = 6.54 \pm 0.12$, $n = 26$). pA_2 values were calculated as described by Arunlakshana and Schild.[30] [b] Potency of yohimbine was taken as unity.

Since evidence has been obtained that presynaptic adrenoceptors[30,31] control the release of acetylcholine from the Auerbach's plexus of the longitudinal muscle strip of the guinea pig ileum, this preparation was also used to study the affinity of compounds for presynaptic α_2-adrenoceptors located on cholinergic axon terminals. Table IV shows the pA_2 values for antagonism of the effects of xylazine and norepinephrine on cholinergic neurotransmission. In this preparation, the berbanes were very potent; the pA_2 values varied from 6.32 (**6h**) to 8.26 (**6d**).

α_1-Adrenoceptor blocking properties for several compounds were also assessed by determination of pA_2 values against the contractile effect of *l*-norepinephrine in the rabbit isolated pulmonary artery. These results are listed in Table V. In this preparation, all of the berbane compounds studied were less potent than standard reference substances; e.g., **6d** was 29 times less potent than idazoxan.

In summary, in the present study the presynaptic α_2-adrenoceptor and postsynaptic α_1-adrenoceptor properties of a series of berbane derivatives were studied and compared with those of idazoxan, yohimbine, phentolamine, and prazosin. Compound **6d** proved to be the most selective antagonist at presynaptic α_2-adrenoceptors and could be considered as a potential antidepressant agent. A number of derivatives have also been prepared that retain some of the potency inherent in **6d**, although with reduced selectivity.

Experimental Section

Chemistry. The IR spectra were recorded on Spectromom 2000, Unicam SP 200, and Perkin-Elmer spectrophotometers. The NMR spectra were obtained with a Perkin-Elmer and a Varian XL-100-15 Fourier-transform instrument, and chemical shifts are reported as ppm (δ) downfield from Me_4Si. Mass spectra were run on an AEI MS902 instrument (70 eV, ion source temperature 150 °C, direct insertion). The reactions were checked by qualitative TLC (KG-PF_{254}, C_6H_6–MeOH, 14:2). For the quantitative separation, Kieselgel $PF_{254-366}$ absorbent (20 × 20 cm, layer 1.5 mm, C_6H_6–MeOH, 14:2) or flash chromatography (Kieselgel G, C_6H_6–MeOH, 14:1) was used. The reactions were carried out under argon, and melting points are uncorrected. Solvents were evaporated under reduced pressure with a rotary evaporator. The experimental data are summarized in Tables I–III.

Ketone Reductions. Methyl [8a*S-(8aα,12aα,13aα)]-11β-Hydroxy-5,6,8a,9,10,11,12,12a,13,13a-decahydro-8*H*-benzo[*g*]-1,3-benzodioxolo[5,6-*a*]quinolizine-12-carboxylate (6a).** Ketone **3a** (0.1 mol) was stirred in CH_2Cl_2 (80 mL) and MeOH (50 mL) in an ice bath, and $NaBH_4$ (10 g, 0.26 mol) was added in small portions over 1 h. After the reaction mixture was stirred for 0.5 h, AcOH (7 mL) was added to the mixture and the solvent was evaporated. The residue was treated with H_2O and basified with 5% Na_2CO_3 to pH 8, and the product was extracted with CH_2Cl_2. The organic phase was evaporated, and the residual hydroxy compound **6a** was crystallized from MeOH. A similar procedure was used to prepare alcohols **6b–d**, **5a,f,b**, **7e,c**, **6g**, and **6k** from the corresponding ketones.

Acetylations. [8a*S-(8aα,12aα,13aα)]-11β-Acetoxy-2,3-dimethoxy-5,6,8a,9,10,11,12,12a,13,13a-decahydro-8*H*-dibenzo[*a*,*g*]quinolizine (6m).** Hydroxyberbane **6l** (1 mmol) was stirred in CH_2Cl_2 (3 mL) with AcCl (2 mmol) at room temperature for 1 day. The solvent was evaporated, and the residue was treated

(30) Arunlakshana, O.; Schild, H. O. *Br. J. Pharmacol. Chemother.* **1959**, *14*, 48.
(31) Paton, W. D. M.; Vizi, E. S. *Br. J. Pharmacol.* **1969**, *35*, 10.
(32) For racemic compounds, only one enantiomer is represented.

with H_2O_2; then the pH was increased to 8 with 5% Na_2CO_3, and the mixture was extracted with Et_2O. After drying ($MgSO_4$), the organic phase was evaporated and the residue was crystallized from MeOH to give **6m**. Compounds **6n** and **6o** were prepared from **6c** and **6d**.

Diols. [8a*S-(8aα,12aα,13aα)]-11β-Hydroxy-12β-(hydroxymethyl)-5,6,8a,9,10,11,12,12a,13,13a-decahydro-8*H*-benzo[*g*]-1,3-benzodioxolo[5,6-*a*]quinolizine (6h).** $NaBH_4$ (20 g, 0.52 mol) was added slowly to keto ester **3a** (0.1 mol) in MeOH (300 mL) and CH_2Cl_2 (50 mL) at room temperature, with continuous stirring. After a further 3 h, AcOH (14 mL) was added dropwise and the solvent was evaporated. The residue was treated with H_2O, basified with 5% Na_2CO_3 to pH 8, filtered, and then separated by flash chromatography to give **6h**. Similarly, **3b** and **2a** were converted to **6i** and **5h**.

[8a*S-(8aα,12aα,13aα)]-11β-Hydroxy-2,3-dihydroxy-5,6,8a,9,10,11,12,12a,13,13a-decahydro-8*H*-dibenzo[*a*,*g*]-quinolizine (6j).** Hydroxy compound **6c** (1 mmol) was stirred with BBr_3 (1.5 g, 6 mmol) in absolute CH_2Cl_2 (50 mL) for 1 day. The solvent was evaporated, and the residue was treated with Me_2CO; then the mixture was filtered, and compound **6j** was recrystallized from EtOH.

Ethyl [8a*S-(8aα,12aα,13aα)]-11β-Hydroxy-5,6,8a,9,10,11,12,12a,13,13a-decahydro-8*H*-benzo[*g*]-1,3-benzodioxolo[5,6-*a*]quinolizine-12-carboxylate (6p).** Hydroxy ester **6a** (1 mmol) was refluxed in EtOH (5 mL) in the presence of 4-$MeC_6H_4SO_3H$ (3 mg) for 5 h. The solvent was evaporated to one-third volume, and the crystalline product was filtered and washed (EtOH) to yield **6p**.

Pharmacology. Preparations. Rat Vas Deferens. Presynaptic α_2-Adrenoceptor Antagonist Properties. The tissue was prepared and set up in an organ bath of 3.5 mL as described by Vizi et al.[29] Cumulative concentration–response curves to xylazine were constructed in the presence and absence of antagonists. The contractions in response to field stimulation[29] were recorded isometrically on a polygraphy. After a 30-min equilibrium period, the cumulative concentration of xylazine was increased. The inhibitory effects were expressed in percentages. The antagonistic potency of the test compounds at α_2-adrenoceptors was expressed in terms of their pA_2 values. These values were obtained from the ratio of the doses of agonist producing 50% of the maximal response in the presence and absence of the test compound, according to the method of Arunlakshana and Schild.[30] The exposure time to antagonists was 20 min.

Longitudinal Muscle Strip. The longitudinal muscle strip of the guinea pig ileum was prepared as described by Paton and Vizi.[31] Guinea pigs of 400–600 g were used. The strips were suspended in organ baths of 3.5 mL and stimulated at 0.1 Hz (1 ms, supramaximal voltage, Biostim, Eltron). *l*-Norepinephrine and xylazine were used as α_2 agonists. The IC_{50} values (concentrations needed to produce 50% inhibition) for *l*-norepinephrine and xylazine were 2×10^{-6} ($n = 12$) and 8.5×10^{-7} M, respectively ($n = 12$). The time of exposure to antagonists was 20 min. The pA_2 values were calculated as described above (four to five tissues were studied at each concentration).

Postsynaptic α_1-Adrenoceptor Antagonist Properties. The rat vas deferens preparation was also used to study the potency of different compounds on postsynaptic α_1-adrenoceptors. Antagonism of *l*-phenylephrine contractions on the vas deferens was studied to determine the pA_2 values. Log dose–response curves were estimated by a curve-fitting program that gave an estimate of the IC_{50} of the agonist.

Pulmonary Artery. A dose–response curve to the contractile effect of *l*-norepinephrine, the endogenous ligand of the α_1-adrenoceptor, in the presence and absence of antagonists was tested on each preparation. The pA_2 values were calculated as described above.

The tissues described above were bathed in Krebs solution (NaCl, 118 mM; KCl, 4.7 mM; $CaCl_2$, 2.5 mM; KH_2PO_4, 1.2 mM; $MgSO_4$, 1.2 mM; $NaHCO_3$, 25 mM; dextrose, 11.2 mM), which was gassed with 95% O_2 and 5% CO_2 and maintained at 37 °C.

Registry No. (±)-**2a**, 108647-35-4; (±)-**2b**, 108647-36-5; (±)-**2c**, 108647-37-6; (±)-**3a**, 108647-32-1; (±)-**3b**, 108647-33-2; (±)-**3c**, 108647-34-3; (±)-**3d**, 108647-40-1; (±)-**3e**, 108647-41-2; (±)-**4a**, 108647-38-7; (±)-**4c**, 108647-39-8; (±)-**5a**, 108647-16-1; (±)-**5b**, 108647-18-3; (±)-**5c**, 108647-19-4; (±)-**5f**, 108647-17-2; (±)-**5h**, 108647-29-6; (±)-**5h**·HCl, 108691-30-1; (±)-**6a**, 108647-12-7; (±)-**6b**, 108647-13-8; (±)-**6c**, 108647-14-9; (±)-**6d**, 108647-15-0; (±)-**6g**, 108647-22-9; (±)-**6h**, 108647-27-4; (±)-**6h**·HCl, 108691-29-8; (±)-**6i**, 108647-28-5; (±)-**6j**, 108647-30-9; (±)-**6j**·HBr, 108691-31-2; (±)-**6k**, 108647-23-0; (±)-**6l**, 108647-42-3; (±)-**6m**, 108647-24-1; (±)-**6n**, 108647-25-2; (±)-**6o**, 108647-26-3; (±)-**6p**, 108647-31-0; (±)-**7c**, 108647-21-8; (±)-**7c**·HCl, 108691-28-7; (±)-**7e**, 108647-20-7.

Aromatase Inhibition by 5-Substituted Pyrimidines and Dihydropyrimidines

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The inhibition of estrogen biosynthesis has been suggested to be an effective treatment of hormone-dependent diseases, particularly breast cancer. Several series of 5-substituted pyrimidine derivatives have been synthesized and tested for their ability to inhibit the enzyme aromatase (estrogen synthetase). Compounds were evaluated in an in vitro assay that measured the inhibition of rat ovarian microsomal aromatase activity. Greatest inhibitory activity was achieved in the cases of diarylpyrimidinemethanols and diarylpyrimidinyl methanes which were substituted in the 4- and 4′-positions with electron-withdrawing substituents, particularly Cl.

Fenarimol [α-(2-chlorophenyl)-α-(4-chlorophenyl)-5-pyrimidinemethanol (**1**)], a pyrimidinylcarbinol fungicide, acts to inhibit ergosterol biosynthesis by inhibiting the P-450 enzyme responsible for 14-demethylation.[1] It has been postulated that the inhibition occurs as a result of the binding of the pyrimidine moiety to the heme portion of the enzyme. As a result of this inhibition, the fungi lack the 14-desmethyl steroids required for the construction of the cell wall.

In reproduction studies in rats, fenarimol caused a dose-related decrease in fertility.[2] The infertility appeared to be a male-specific effect and was associated with a decrease in male sexual behavior. In the rat, gonadal androgens are metabolized to estrogens within the central nervous system (CNS) via the P-450 enzyme aromatase

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