Lysergic Acid and Quinidine Analogs. 2-(*o*-Acylaminophenethyl)piperidines

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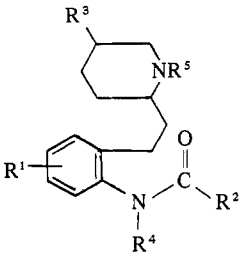
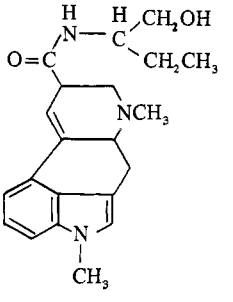
The synthesis of 2-(*o*-acylaminophenethyl)piperidines (I) and related compounds as open-chain analogs of lysergic acid and quinidine is reported. Several of these compounds demonstrated potent antiserotonin activity and antiarrhythmic action in primary pharmacological screening tests.

We wish to report a series of piperidines, I, which have been prepared as open-chain analogs of the lysergic acid derivative, methysergide (II), for use as potential prophylactic agents for vascular headache. In our model we have opened the C ring of the lysergic acid molecule. The indole nucleus also has been replaced with an anilide moiety.

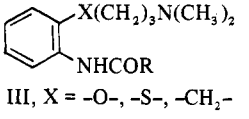


I

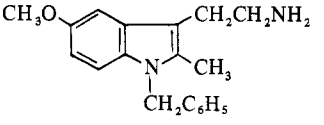


II

This latter analogy was drawn from the observation that the compounds (III, X = -S-) of Krapcho,[1] which contain an anilide moiety, were shown to have pharmacological activity similar to 1-benzyl-2-methyl-3-(2-aminoethyl)-5-methoxyindole hydrochloride IV. Recently Drain[2] pre-

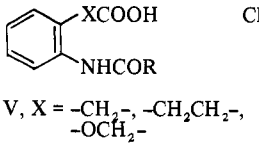


III, X = -O-, -S-, $-CH_2-$

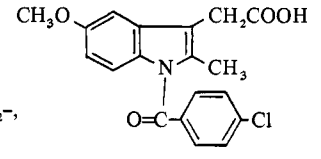


IV

pared active analogs (V, X = $-OCH_2-$) of indomethacin (VI) in which the indole nucleus was replaced by an anilide group.



V, X = $-CH_2-$, $-CH_2CH_2-$, $-OCH_2-$

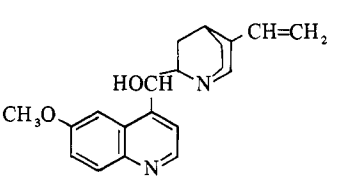


VI

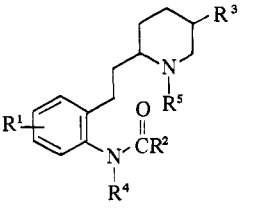
Since the activity of methysergide (II) has been attributed to its strong antiserotonin effects,[3,4] an *in vitro* antiserotonin test was used as a convenient guide in assessing the physiological activity of this series (I).

Several derivatives of I exhibited antiserotonin activity equivalent to II. This is in contrast to results recently summarized by Campaigne and Knapp.[5] In their review of structural analogs of lysergic acid and their antiserotonin activity, relatively few analogs were reported with activities approaching the potency range of the parent compound. Based on the preliminary screening data, compounds **29**, **36–38**, **43**, and **46** have been selected for further evaluation.

It is interesting also that several of the piperidines I are more potent than quinidine (VII) as antiarrhythmic agents. A comparison of the structure of I with that of VII suggests that possibly the anilide moiety of I in this instance can serve the same biological role as does the quinoline nucleus



VII

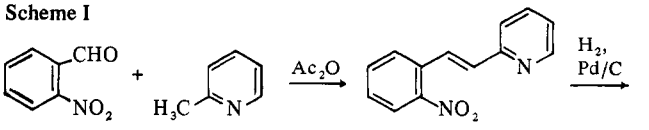


I

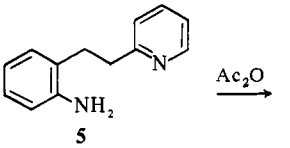
of VII. Those selected for further evaluation based on the preliminary screening data include compounds **42** and **49–52**.

Chemistry. The synthesis of all the compounds begins with the preparation of a 2-styrylpyridine (Table I) as outlined in Schemes I and II. If R^2 on the final product I is

Scheme I



1



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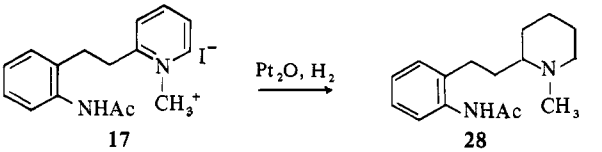
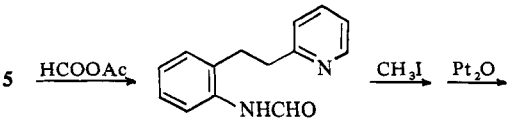


17 28

Scheme II



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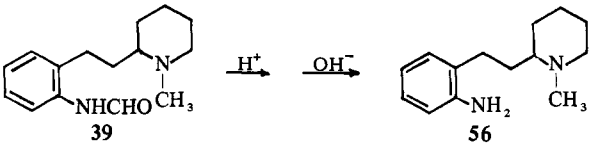
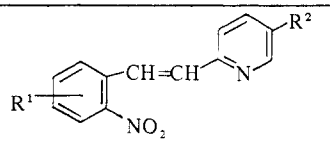


39 56

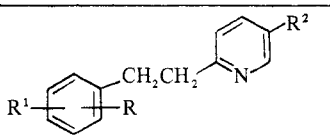
Table I. 2-Styrylpyridines



No.	R^1	R^2	Mp, °C[a]	Yield, %	Recrystn solvents[b]	Formula	Analyses
1	H	H	98-99[d]	62	A	$C_{13}H_{10}N_2O_2$	*c*
2	H	$-C_2H_5$	52.5-54.5	32	A	$C_{15}H_{14}N_2O_2$	C, H, N
3	5-OCH_3	H	86.5-87.5	58	C, D	$C_{14}H_{12}N_2O_3$	C, H, N
4	H	$-CON(C_2H_5)_2$	145-147	75	E	$C_{18}H_{19}N_3O_3$	C, H, N

[a]All melting points are corrected unless indicated otherwise. [b]A, *i*-Pr_2O; B, DMF; C, heptane; D, methylcyclohexane; E, EtOH. [c]Reference 6. [d]Not corrected.

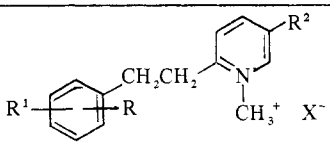
Table II. 2-Phenethylpyridines



No.	R	R^1	R^2	Bp (mm) or mp, °C[a]	Yield, %	Recrystn solvents[b]	Formula	Analyses	Method[d]
5	2-NH_2	H	H	59-61[e]	89	A	$C_{13}H_{14}N_2$	*c*	A
6	2-NHAc	H	H	68-71[e]	98		$C_{15}H_{16}N_2O$	*c*	B
7	2-NH_2	H	$-CONEt_2$	224-226	36	C	$C_{18}H_{23}N_3O \cdot 2HCl$	C, H, N	A
8	2-NH_2	H	Et	52.5-53.5	77	A + B	$C_{15}H_{18}N_2$	C, H, N	A
9	2-NHCHO	H	Et	62-63.5	70	A	$C_{16}H_{18}N_2O$	C, H, N	B
10	2-NHCHO	H	H	83-83.5	83	D	$C_{14}H_{14}N_2O$	C, H, N	B
11	2-NH_2	5-OCH_3	H	77.5-78.5	78	C + D + E	$C_{14}H_{16}N_2O \cdot H_2O$	C, H, N	A
12	2-NHCHO	5-OCH_3	H	93.5-94	71	D	$C_{15}H_{16}N_2O_2$	C, H, N	B
13	2-Phthalimido	H	H	88.5-92.5	71	C	$C_{21}H_{16}N_2O_2 \cdot H_2O$	C, H, N	C
14	2-NHAc	H	$-CONEt_2$		89		$C_{20}H_{25}N_3O_2$	*f*	B
15	3-OCH_3	H	H	147-151 (0.1)	87		$C_{14}H_{15}NO$	C, H, N	A
16	2-NHCHO	H	$-CONEt_2$				$C_{19}H_{23}N_3O_2$	*f*	B

[a]All melting points are corrected unless indicated otherwise. [b]A, *i*-Pr_2O; B, heptane; C, EtOH; D, *i*-PrOAc; E, H_2O. [c]D. H. Hey and J. M. Osbond, *J. Chem. Soc.*, 3164 (1949). [d]See Experimental Section. [e]Uncorrected melting point. [f]Used crude.

Table III. 2-Phenethylpyridinium Halides

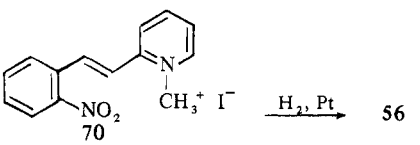


No.	R	R^1	R^2	X	Mp, °C[a]	Yield, %	Recrystn solvents[b]	Formula	Analyses	Method[c]
17	2-NHAc	H	H	I	229.5-231.5	60	A	$C_{16}H_{19}IN_2O$	C, H, N	A
18	2-NHAc	H	$-CONEt_2$	I	134.5-139	30	B + C	$C_{21}H_{28}IN_3O_2$	C, H, N	A
19	2-NHAc	H	$-CONEt_2$	Cl	100-102.5	57	B + C	$C_{21}H_{28}ClN_3O_2 \cdot 2H_2O$	C, H, N	B
20	3-OCH_3	H	H	I	177.5-180	66	*d*	$C_{15}H_{18}INO$	C, H, N	A
21	2-NHCHO	H	$-C_2H_5$	I	134.5-136.5	74	*d*	$C_{17}H_{21}IN_2O$	C, H, N	A
22	2-NHCHO	H	H	I	199.5-201.5	92	*d*	$C_{15}H_{17}IN_2O$	C, H, N	A
23	2-NHCHO	5-OCH_3	H	I	184-186.5	95	*d*	$C_{16}H_{19}IN_2O_2$	C, H, N	A
24	2-NHCHO	H	$-CONEt_2$	I				$C_{20}H_{26}IN_3O_2$	*e*	A
25	2-NHCHO	H	$-CONEt_2$	Cl				$C_{20}H_{26}ClN_3O_2$	*e*	B
26	2-NHCHO	H	$-C_2H_5$	Cl		94		$C_{17}H_{21}ClN_2O$	*e*	B

[a]All melting points are corrected unless indicated otherwise. [b]A, EtOH; B, H_2O; C, Me_2CO. [c]See Experimental Section. [d]Pure product crystallizes from the reaction. [e]The compound is a gum. No attempt was made to attain analytical purity.

stable toward catalytic reduction, Scheme I, as illustrated by the preparation of **28**, can be followed. However, it is more convenient to prepare the diamine **56** as illustrated by Scheme II through the phenethylpyridines (Table II). The diamine **56** can then be treated with a variety of reagents to provide the compounds of Table IV.

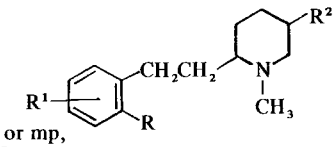
A more direct route to **56** would be reduction of the styryl quaternary compound **70**[6] directly to **56**, but **70** was difficult to reduce completely, so we used the route outlined in Scheme II.



70 **56**

Reduction of the 2-phenethylpyridinium salts (Table III) is more difficult if the 5 position of the pyridine ring is substituted. As an example, the pyridinium iodide **21** is resistant to catalytic reduction. The difficulty was eliminated

Table IV. 2-Phenethylpiperidines

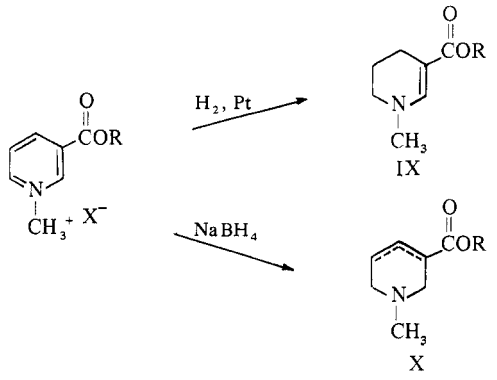


No.	R	R¹	R²	Bp (mm) or mp, °C[a]	Yield, %	Recrystn solvents[b]	Formula	Analyses	Method[c]
27	NH_2	H	H	268.5–271.5	70	A + G	$C_{14}H_{22}N_2 \cdot 2HCl$	C, H, N	A
28	NHAc	H	H	173.5–174.5	76	C	$C_{16}H_{24}N_2O \cdot 0.5C_6H_{10}O_8$[d]	C, H, N	C
29	Cinnamamido	H	H	101.5–103.5	70	A	$C_{23}H_{28}N_2O$	C, H, N	B
30	$NHSO_2Me$	H	H	91.5–93.5	41	C, H	$C_{15}H_{24}N_2O_2S$	C, H, N	B
31[f]	NHAc	H	-$CONEt_2$	*n*	7.2		$C_{21}H_{33}N_3O_2$	C, H, N	D
32[f]	NHAc	H	-$CONEt_2$	*n*	29		$C_{21}H_{33}N_3O_2$	C, H, N	D
33[f]	Cinnamamido	H	-$CONEt_2$	158–164	13	A + C	$C_{28}H_{37}N_3O_2 \cdot C_9H_8O_2$[g]	C, H, N	B
34[h]	OMe	H	H	147.5–149.5	65	C	$C_{15}H_{23}NO \cdot HI$	C, H, N	A
35[h]	OH	H	H	183.5–185	65	C	$C_{14}H_{21}NO \cdot HBr$	C, H, N	E
36[e]	Cinnamamido	H	Et	184–187	65	E	$C_{25}H_{32}N_2O \cdot HCl$	C, H, N	B
37[f]	Cinnamamido	H	Et	91–98	40	D, F	$C_{25}H_{32}N_2O \cdot H_2O$	C, H, N, H_2O	B
38	α-Methylcinnamamido	H	H	154.5–156.5	47	C + H	$C_{24}H_{30}N_2O \cdot 0.5C_6H_{10}O_8$[d]	C, H, N	B
39	NHCHO	H	H	81–84.5	79	A + B	$C_{14}H_{22}N_2O$	C, H, N	C
40	*N*-Methylcinnamamido	H	H	174–175	69	G	$C_{24}H_{30}N_2O \cdot 0.5C_6H_{10}O_8$[d]	C, H, N	B
41	Cinnamamido	5-OMe	H	126.5–127.5	38	D	$C_{24}H_{30}N_2O_2$	C, H, N	B
42	*p*-Methoxybenzamido	H	H	131.5–132.5	63	B, D	$C_{22}H_{28}N_2O_2$	C, H, N	B
43	Cinnamamido	H	-$CONEt_2$	117–120	10	G	$C_{28}H_{37}N_3O_2 \cdot 0.5C_6H_{10}O_8$[d]	H, N; C[i]	B
44	3,4-Dimethoxybenzamido	H	H	123–124.5	64	C + E	$C_{23}H_{30}N_2O_3$	C, H, N	B
45	3,5-Dimethoxybenzamido	H	H	140.5–142	88	A + C	$C_{23}H_{30}N_2O_3 \cdot C_4H_4O_4$[j]	C, H, N	B
46	*p*-Chlorobenzamido	H	H	130–131	68	A + D	$C_{21}H_{25}ClN_2O$	C, H, N	B
47	*m*-Methoxybenzamido	H	H	124.5–126.5	43	G, H	$C_{22}H_{28}N_2O_2$	C, H, N	B
48	3,4,5-Trimethoxybenzamido	H	H	115–122	63	E + G	$C_{24}H_{32}N_2O_4 \cdot 0.5C_6H_{10}O_8 \cdot H_2O$[d]	C, H, N	B
49	2-Benzamido	H	H	85.5–87	37	A, E + G	$C_{21}H_{26}N_2O$	C, H, N	B
50	*p*-Acetoxybenzamido	H	H	88–108[p]	26	A, D	$C_{23}H_{28}N_2O_3$	C, H, N	B
51	*p*-Hydroxybenzamido	H	H	178.5–182.5	16	J	$C_{21}H_{26}N_2O_2$	C, H, N	
52	*p*-Aminobenzamido	H	H	147–148.5	66	K	$C_{21}H_{27}N_3O$	C, H, N	I
53	2-Thiophenecarboxamido	H	H	143.5–146	32	C + H	$C_{19}H_{24}N_2OS \cdot 0.5C_6H_{10}O_8$	C, H, N, S	B
54	4-(Methylthio)benzamido	H	H	145–145.5	60	H	$C_{22}H_{28}N_2OS$	C, H, N	B
55	*p*-Nitrobenzamido	H	H	162–163.5	71	H	$C_{21}H_{25}N_3O_3$	C, H, N	B
56	NH_2	H	H	121–125 (0.04)	87		$C_{14}H_{22}N_2$	C, H, N	A
57	NHAc	H	-$CONEt_2$		75		$C_{21}H_{33}N_3O_2$	*m*	D
58	NHCHO	H	-$CONEt_2$		82[k]		$C_{20}H_{31}N_3O_2$	*m*	D, H
59	NH_2	H	-$CONEt_2$		70		$C_{19}H_{31}N_3O$	*m*	F
60	NHCHO	H	Et		88		$C_{17}H_{26}N_2O$	*m*	D
61[f]	NHCHO	H	Et	174–176	31	C	$C_{17}H_{26}N_2O \cdot C_2H_2O_4$	C, H, N	D
62[e]	NH_2	H	Et	139–147.5	19	A + C	$C_{16}H_{26}N_2 \cdot 2HCl$	H, N; C[l]	F
63[f]	NH_2	H	Et		98		$C_{16}H_{26}N_2$	*m*	F
64	NHMe	H	H	150–155 (0.05)	88		$C_{15}H_{24}N_2$	C, H, N	G
65	NHCHO	5-OMe	H				$C_{16}H_{24}N_2O_2$	*m*	C
66	NH_2	5-OMe	H				$C_{15}H_{24}N_2O$	*m*	F
67[e]	NH_2	H	-$CONEt_2$		51[o]		$C_{19}H_{31}N_3O$	*m*	H
68[f]	NH_2	H	-$CONEt_2$		27[o]		$C_{19}H_{31}N_3O$	*m*	D

[a]All melting points are corrected unless indicated otherwise. [b]A, *i*-Pr_2O; B, heptane; C, EtOH; D, *i*-PrOAc; E, H_2O; F, Me_2CO; G, MeOH; H, EtOAc; I, *i*-PrOH; J, 95% EtOH; K, CH_3CN. [c]See Experimental Section. [d]Mucate salt. [e]A racemate; see Experimental Section. [f]B racemate; see Experimental Section. [g]Cinnamate salt. [h]Reference 12. [i]C: calcd, 67.36; found, 66.57. [j]Maleate salt. [k]By method H. [l]C: calcd, 60.18; found, 57.86. [m]The compound is an oil. No attempt was made to attain analytical purity. [n]The compound is a glass at 25°. [o]Yield given for the chromatographic isolation. [p]The broad melting point is due to polymorphism.

by converting **21** to the chloride **26** (not isolated) which was easily reduced to the piperidine **60**. Conversion of the iodide **18** to the chloride **19** also facilitated catalytic hydrogenation to the piperidine **57**.

Unlike these two examples, the pyridine ring of the crude pyridinium chloride **25** could not be hydrogenated completely by catalytic means to the piperidine **58**. A mixture containing about 40% of unsaturated material (nmr) was always obtained and purification was difficult. Reduction of pyridine and pyridinium quaternary salts of type VIII commonly stops at the tetrahydro stage (IX) because of the formation of a vinylogous amide.[7] A chemical reduction of VIII with $NaBH_4$ gives a mixture of two tetrahydropyridines of type X. Neither is a vinylogous amide. Consequently, catalytic reduction of type X compounds occurs readily. Therefore, **25** was partially reduced with $NaBH_4$. The reduction was completed catalytically to give the desired piperidine **58**.



When R^3 in the general formula I is other than H, the compounds exist in two racemic modifications. These racemates were separated by either fractional recrystallization or by chromatography. In Table IV the nomenclature "A racemate" or "B racemate" is used to differentiate these racemates. The A racemate is always the one with the larger R_f in tlc. See the Experimental Section for details of the separation of these racemates.

Biological Activity. Antiserotonin Activity. Two general screening tests were used to evaluate the antiserotonin activity of these compounds. These are the *in vitro* inhibition of serotonin-induced spasm of rat uterine tissue as compared to the test compound's antagonism to spontaneous rat uterine activity[8] and the *in vivo* inhibition of 5-HTP-parnate-induced head twitch in the mouse.[9] The observed activity of the members of this series is listed in Table V.

Antiarrhythmic Activity. Ventricular arrhythmia is produced in mice by chloroform inhalation. The ED_{50} of the test compound necessary to prevent this arrhythmia is determined.[10] Most benzanilides of this series are active in this test. They are listed in Table VI.

Experimental Section

General Procedures. A Thomas-Hoover capillary melting point apparatus was used for all melting point determinations. The melting points are corrected unless indicated otherwise. Analyses indicated only by symbols of the elements are within ±0.4% of theoretical values. The structures of intermediates which were not analyzed were characterized by ir, nmr, or tlc.

2-Styrylpyridines. The 2-styrylpyridines were prepared by a known method.[6] The yields were improved by quadrupling the reaction time.

2-Phenethylpyridines. Method A. 2-(*o*-Aminophenethyl)-5-ethylpyridine (8). 5-Ethyl-2-(*o*-nitrostyryl)pyridine (**2**, 25 g, 0.098 mol) was hydrogenated on a Parr shaker (10% Pd/C, EtOH). Recrystallization from *i*-Pr_2O-heptane gave 17.1 g (77%), mp 52.5–53.5°. *Anal.* ($C_{15}H_{16}N_2$) C, H, N.

Table V. Antiserotonin Activity

	Rat uterine tissue					
	5-HT-induced spasm		Spont activity		5-HTP-parnate head twitch	
No.	IC_{50}, μg/ml[a]	95% conf limits	IC_{50}, μg/ml[a]	95% conf limits	ED_{50}, mg/kg ip	95% conf limits
27	6.7	0.36–1.25	809	514–1274	Inactive	
28	28.5	7.7–106	>1000		Inactive	
29	0.0018	0.0005–0.0059	27.9	21.9–35.6	21.0	13.7–32.1
30	20.6	10.9–38.9	810	657–1000	Inactive	
31	5.4	3.1–9.4	>1000		nt[b]	
32	831	277–2494	>200		Inactive	
33	0.1	0.02–0.5	8.2	6.3–10.8	>1000	
34	1.7	0.4–6.6	>100		Inactive	
35	6.0	1.8–19.7	>100		>50	
36	0.013	0.011–0.014	5.3	2.1–13.5	15.5	12.1–19.8
37	0.02	0.007–0.08	114	46–287	Inactive	
38	0.027	0.02–0.035	36.2	24.4–53.8	>25	
39	0.72	0.47–1.10	>160		Inactive	
40	0.15	0.05–0.42	23	17.1–30.8	>50	
41	0.051	0.027–0.096	7.6	3.6–15.9	Inactive	
42	0.0055	0.0049–0.0061	128	88–187	Inactive	
43	0.04	0.026–0.065	23	16.6–32.6	8.8	3.8–20.2
44	0.05	0.029–0.09	>128		Inactive	
45	0.9	0.7–1.1	>10		>25	
46	0.0075	0.0066–0.0086	>100		10.0	4.6–22.0
47	0.45	0.31–0.67	>10		Inactive	
48	1.36	1.04–1.77	>10		Inactive	
49	0.24	0.17–0.35	>100		>10	
50	0.028	0.023–0.035	>100		Inactive	
51	0.056	0.053–0.060	>100		nt[b]	
52	0.236	0.207–0.269	>160		Inactive	
53	0.06	0.04–0.08	>640		Inactive	
54	0.005	0.004–0.006	109	92–128	Inactive	
Methysergide	0.0025	0.0004–0.0129	26.9	8–90	24.1	9.6–60

[a] IC_{50} values (concentration causing 50% reduction in induced or spontaneous activity) and associated statistical variations were derived from calculated log dose-response curves employing 3–8 trials at each of 2–4 concentrations for each compound. [b] Not tested due to insufficient compound.

Table VI. Antiarrhythmic Activity

No.	ED_{50}, mg/kg ip	95% conf limits	Times quinidine
27	Inactive		
28	>50		
29	Inactive		
30	nt[a]		
31	nt[a]		
32	nt[a]		
33	nt[a]		
34	>100		<0.12
35	nt[a]		
36	36.5	25.5-52.2	2.3
37	Inactive		
38	14	8.7-22.4	6
39	nt[a]		
40	25	15.0-40.0	3.3
41	32	24.0-42.6	2.6
42	7.1	5.25-9.58	12
43	25	15.0-40.0	3.3
44	10	6.7-15.0	8.3
45	>50		<1.6
46	>25		<3.3
47	10	6.9-14.5	8.3
48	39	34.6-52.6	2.1
49	7.2	4.8-10.8	12
50	2.8	1.75-4.76	29
51	1.7	0.9-3.1	49
52	4.0	2.4-6.7	21
53	>10		<8.3
54	>25		<3.3
Quinidine sulfate	83	42-117	1

[a]Not tested due to insufficient compound.

Method B. 5-Ethyl-2-(o-formamidophenethyl)pyridine (9). 2-(o-Aminophenethyl)-5-ethylpyridine (**8**, 8.2 g, 0.037 mol) was formylated with 45 ml of acetic-formic anhydride.[11] A basic work-up followed by recrystallization from *i*-Pr_2O yielded 6.5 g (70%), mp 62-63.5°. *Anal.* ($C_{16}H_{18}N_2O$) C, H, N.

Method C. 2-(o-Phthalimidophenethyl)pyridine (13). A mixture of 2-(o-aminophenethyl)pyridine (**5**, 17.6 g, 0.089 mol), phthalic anhydride (13.2 g, 0.089 mol), and 200 ml of dry xylene was heated to reflux in a flask fitted with a Dean-Stark trap. A short time after solution a gum separated which redissolved by the time the theoretical amount of H_2O was collected. The xylene was evaporated and the residue was crystallized from 95% EtOH as the monohydrate: yield, 21.8 g (71%); mp 88.5-92.5°. *Anal.* ($C_{21}H_{16}N_2O_2 \cdot H_2O$) C, H, N.

Phenethylpyridinium Halides. Method A. 2-(o-Formamidophenethyl)-1-methylpyridinium Iodide (22). A solution of 2-(o-formamidophenethyl)pyridine (**10**, 55 g, 0.243 mol), MeI (38 g, 0.268 mol), and acetone (500 ml) was refluxed for 20 hr. The product crystallized from the hot solution: yield, 82 g (92%); mp 199.5-201.5°. *Anal.* ($C_{15}H_{17}IN_2O$) C, H, N.

Method B. 5-Ethyl-2-(o-formamidophenethyl)-1-methylpyridinium Chloride (26). A solution of 5-ethyl-2-(o-formamidophenethyl)-1-methylpyridinium iodide (**21**, 35.4 g, 0.089 mol) in 500 ml of H_2O was converted to the chloride by passage through a 40 × 2.5 cm column of Dowex 21-K, Cl^- (150 mequiv, 50-100 mesh). The evaporated eluate yielded 25.5 g (95%) of crude product which was used without further purification.

Phenethylpiperidines. Method A. 2-(o-Aminophenethyl)-1-methylpiperidine (56). 2-(o-Nitrostyryl)-1-methylpyridinium iodide[6] (40.5 g, 0.11 mol) was hydrogenated on a Parr shaker (PtO_2, EtOH). A basic work-up followed by distillation gave 20.8 g (87%), bp 121-125° (0.04 mm). *Anal.* ($C_{14}H_{22}N$) C, H, N.

Method B. 2'-[2-(1-Methyl-2-piperidyl)ethyl]cinnamanilide (29). 2-(o-Aminophenethyl)-1-methylpiperidine (**56**, 7.8 g, 0.036 mol) in pyridine (100 ml) was acylated with cinnamoyl chloride (6.0 g, 0.036 mol). A basic work-up gave the crude product which was twice recrystallized from *i*-Pr_2O: yield, 8.7 g (70%); mp 101.5-103.5°. *Anal.* ($C_{23}H_{28}N_2O$) C, H, N.

Method C was the same as method A except that purification was by recrystallization or salt formation.

Method D. The pyridinium quaternary iodides were converted to the chlorides by ion exchange on Dowex 21-K (Cl^-) resin and then reduced according to method C.

Method E. 2-(o-Hydroxyphenethyl)-1-methylpiperidine Hydrobromide (35).[12] A solution of 2-(o-methoxyphenethyl)-1-methylpiperidine hydriodide (**34**, 6 g, 0.017 mol) in 48% HBr (100 ml) was refluxed for 16 hr. The solution was concentrated. The product crystallized and was twice recrystallized from EtOH: yield, 3.2 g (65%); mp 183.5-185°. *Anal.* ($C_{14}H_{21}NO \cdot HBr$) C, H, N.

Method F. 6-(o-Aminophenethyl)-*N,N*-diethyl-1-methylpiperidine-3-carboxamide (59). A solution of crude 6-(o-formamidophenethyl)-*N,N*-diethyl-1-methylpiperidine-3-carboxamide (**58**, 28 g, 0.081 mol) in methanolic HCl (1 *N*, 500 ml) was allowed to stand 18 hr at 25°. The solvent was evaporated. A basic work-up yielded 17.9 g (70%) of crude product which was pure enough for use as an intermediate.

Method G. 2-(o-Methylaminophenethyl)-1-methylpiperidine (64). 2'-[2-(1-Methyl-2-piperidyl)ethyl]formanilide (**39**, 20 g, 0.082 mol) was reduced with $LiAlH_4$ (THF) and worked up in the usual way. Distillation of the crude product gave 16.6 g (88%), bp 150-155° (0.05 mm). *Anal.* ($C_{15}H_{24}N_2$) C, H, N.

Method H. *N,N*-Diethyl-6-(o-formamidophenethyl)-1-methylpiperidine-3-carboxamide (58). To a solution of 5-diethylcarbamyl-2-(o-formamidophenethyl)-1-methylpyridinium chloride (**25**, 37.6 g, 0.1 mol) in 300 ml of methanol was added 50% NaOH (9.6 g, 0.12 mol) in 45 ml of H_2O. $NaBH_4$ (4.56 g, 0.12 mol) was added in portions, with stirring. The solution was allowed to stand 2 hr and evaporated. Water (500 ml) was added to the residue and the mixture was extracted (Et_2O). The extracts were washed (H_2O, brine), dried ($MgSO_4$), and evaporated to give the crude tetrahydro compound which was immediately hydrogenated (10% Pd/C, EtOH) on a Parr shaker. The crude product from the reduction was pure enough for use as an intermediate.

Method I. 4-Amino-2'-[2-(1-methyl-2-piperidyl)ethyl]benzanilide (52). 2'-[2-(1-Methyl-2-piperidyl)ethyl]-4-nitrobenzanilide (**55**, 6.5 g, 0.018 mol) was hydrogenated on a Parr shaker (10% Pd/C, EtOH). Recrystallization from CH_3CN gave 3.9 g (66%), mp 147-148.5°. *Anal.* ($C_{21}H_{27}N_3O$) C, H, N.

***N,N*-Diethyl-6-methylnicotinamide (69).**[13] To a vigorously stirred suspension of 6-methylnicotinic acid (51 g, 0.373 mol) in 500 ml of toluene was added diethylamine (115 ml, 82 g, 1.12 mol). To the resulting solution was added P_2O_5 (150 g, 1.12 mol), and the mixture was refluxed for 2 hr. The toluene was decanted. The residual gum was dissolved in 1500 ml of H_2O and the solution was basified with 40% NaOH while holding the temperature below 40°. The solution was saturated with NaCl and extracted (Et_2O). The ethereal extract was dried ($MgSO_4$). Evaporation furnished the crude product which was distilled: yield, 50.0 g (70%); bp 106° (0.05 mm) [lit. bp 160-164° (12 mm)].

Separation of Racemates. Separation of the A (31) and B (32) Racemates of 6-(o-Acetamidophenethyl)-*N,N*-diethyl-1-methylpiperidine-3-carboxamide (57). Crude 6-(o-acetamidophenethyl)-*N,N*-diethyl-1-methylpiperidine-3-carboxamide (**57**, 10.8 g) was chromatographed on 300 g of silica gel. The column was eluted with solvents of increasing polarity beginning with C_6H_6, through EtOH-EtOAc-NH_4OH mixtures, and ending with EtOH + 0.5% of 58% NH_4OH. Chromatographically pure A racemate (2.4 g) and B racemate (5.9 g) were obtained. (In this and following separations, the racemate with the smaller R_f is designated B.) The progress of development and the purity of the separated racemates were determined by tlc (silica gel, EtOH + trace NH_4OH). Both the A and B racemates are extremely viscous oils. Traces of solvent were removed by distillation in a sublimator at 0.02 mm: yield of A, 1.3 g [*Anal.* ($C_{21}H_{33}N_3O_2$) C, H, N]; yield of B, 5.2 g [*Anal.* ($C_{21}H_{33}N_3O_2$) C, H, N].

Isolation of the A Racemate (67) of 6-(o-Aminophenethyl)-*N,N*-diethyl-1-methylpiperidine-3-carboxamide. Crude 6-(o-aminophenethyl)-*N,N*-diethyl-1-methylpiperidine-3-carboxamide (**59**, 10 g), reduced by method H, was chromatographed by the dry column technique[14] (1 kg of silica gel, 95% EtOH + 1% of 58% NH_4OH). Pure A (5.1 g) and B (4.1 g) contaminated with A (tlc, silica gel, EtOH + trace NH_4OH) were obtained.

Isolation of the B Racemate (68) of 6-(o-Aminophenethyl)-*N,N*-diethyl-1-methylpiperidine-3-carboxamide. Crude 6-(o-aminophenethyl)-*N,N*-diethyl-1-methylpiperidine-3-carboxamide (11 g), reduced by method D, was chromatographed in the same way as **57**. Chromatographically pure B racemate (3.0 g) and impure A (5.5 g) (nmr indicates contamination with an unsaturated impurity) were obtained.

Isolation of the A (62) and B (63) Racemates of 2-(o-Aminophenethyl)-5-ethyl-1-methylpiperidine. Crude 2-(o-formamidophenethyl)-5-ethyl-1-methylpiperidine (**60**, 19.8 g, 0.072 mol), prepared by method D, was treated with a solution of oxalic acid dihydrate (9.2 g, 0.072 mol) in 200 ml of EtOH. An oxalate salt

crystallized. It was rich in the B racemate. Two more recrystallizations from EtOH afforded pure B racemate: yield, 8.2 g (31%); mp 178–179.5°. *Anal.* ($C_{17}H_{26}N_2O_2 \cdot C_2H_2O_4$) C, H, N.

This oxalate salt was converted to the free base. The formyl group was removed by the technique described in method F. The usual work-up gave the B racemate **(63)** of 2-(*o*-aminophenethyl)-5-ethyl-1-methylpiperidine (5.5 g, 98%) as an oil which was pure enough for use as an intermediate.

The mother liquor from the preparation of the oxalate salt was evaporated. The residue was recrystallized from *i*-PrOH. A solid (1.8 g) was obtained which tlc indicated to be a mixture of A and B racemates. The solid was discarded. Evaporation of the mother liquor gave a crystalline residue rich in the A racemate. It was converted to 6.7 g of free base. The formyl group was removed by the technique described in method F to give a crystalline dihydrochloride. Recrystallization from *i*-PrOH and then EtOH–*i*-Pr_2O gave material which was approximately 90% A and 10% B (tlc, silica gel, EtOH + trace NH_4OH). *Anal.* ($C_{16}H_{26}N_2 \cdot 2HCl$) H, N; C: calcd, 60.18; found, 57.86. This salt was converted to 3.3 g (19%) of free base. It was pure enough for use as an intermediate.

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β-Adrenergic Blocking Agents. 14. Microbiological Reduction of Isopropylaminomethyl 2-Naphthyl Ketone to (*R*)-(−)-2-Isopropylamino-1-(2-naphthyl)ethanol and Related Reductions

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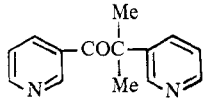
Isopropylaminomethyl 2-naphthyl ketone **(3)** is reduced by *B. theobromae* to (*R*)-(−)-2-isopropylamino-1-(2-naphthyl)ethanol **(4)** of optical purity 89% in low (6.5%) yield. The major metabolic pathway is *via* 2-naphthylglyoxal **(9)**, which leads to the isolable products (*R*)-(−)-2-naphthylglycolic acid **(6)** and (*S*)-(+)-(2-naphthyl)ethane-1,2-diol **(5)**, both of optical purity >95%.

It has been shown previously that 2-methyl-1,2-di(3-pyridyl)-1-propanone **(1)** (metyrapone, SU-4885) is reduced with ~99% stereospecificity by the organism *Botryodiplodia theobromae Pat.* to give (−)-2-methyl-1,2-di(3-pyridyl)-1-propanol **(2)** in good yield.[1] The absolute configuration of the product is not known. It was of interest to find out whether this organism would convert isopropylaminomethyl 2-naphthyl ketone **(3)**[2] to an optically active form of the β-adrenergic blocking agent 2-isopropylamino-1-(2-naphthyl)ethanol **(4)**[2] (pronethalol). The pharmacologically active (−) isomer of pronethalol has the *R* configuration.[3]



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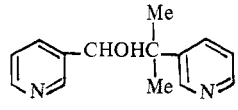

2

The ketone **3** was incubated with the organism in shake flasks. Fermentation was stopped after 2 days when samples monitored by tlc showed the absence of substrate. Extraction of the fermentation and separation of the products gave one basic, one neutral, and one acidic metabolite. The basic metabolite, which proved to be pronethalol **4**, gave a hydrochloride, $[\alpha]^{21}D$ −46.8°. Optically pure (−)-pronethalol hydrochloride has $[\alpha]^{21}D$ −52.6°,[3] and so the material produced by the organism had an optical purity of 89%,[4] *i.e.*, an *R*-(−) isomer content of 94%. The yield was low (6.5%). The neutral metabolite was (+)-1-(2-naphthyl)ethane-1,2-diol **(5)**, $[\alpha]^{21}D$ +32.4°, of uncertain optical purity. The acid metabolite (≃16% yield) was (−)-2-naphthylglycolic acid **(6)**, $[\alpha]^{21}D$ −142.2°, also of uncertain optical purity. In a separate experiment 2-naphthoic acid **(7)** was identified as a minor metabolite. The two acidic metabolites are produced from pronethalol by the guinea pig, rabbit, and rat.[5] Diols are known to be metabolites of 1-aryl-2-aminoethanols such as epinephrine.[6]

Comparison of the optical data for the diol **5** and the glycolic acid **6** with data for the phenyl analogs, 1-phenylethane-1,2-diol (**5**, R = phenyl) and mandelic acid (**6**, R = phenyl), showed that the diol and the acid differed in absolute configuration. (*R*)-(−)-Mandelic acid, $[\alpha]^{24}D$ −152.3°, is reduced by $LiAlH_4$ to (*R*)-(−)-1-phenylethane-1,2-diol, $[\alpha]^{25}D$ −39.7°, without racemization.[7] The fermentation glycolic acid **6** and the fermentation diol **5** differ in sign of rotation. That they differ in absolute configuration was confirmed by converting the acid **6**, $[\alpha]^{21}D$ −142.2°, to its methyl ester, $[\alpha]^{21}D$ −133.1°, which by $LiAlH_4$ reduction gave the chemically produced diol **5**, $[\alpha]^{21}D$ −33.7°. Although the optical data were not all measured in the same solvent, the sign and magnitude of the optical rotations and the considerable shift in the same direction for the change acid → diol strongly suggest that (−)-2-naphthylglycolic acid and (−)-1-(2-naphthyl)ethane-1,2-diol have the *R* con-