$(CH_2)_2OSO_2CH_3$, 61439-60-9; n-C_4H_9NCO, 111-36-4; cyclohexanone, 108-94-1; ethylene oxide, 75-21-8; 1-[4-(oxiranylmethoxy)phenyl]ethanone, 19152-55-7; 4-vinylpyridine, 100-43-6; *N*-(chloroacetyl)piperidine, 1440-60-4; ethyl 4-[[[(2-amino-4-fluorophenyl)amino]thioxomethyl]amino]-1-piperidinecarboxylate, 73733-85-4; ethyl 4-[[[[5-chloro-2-[[(4-fluorophenyl)methyl]amino]phenyl]amino]thioxomethyl]amino]-1-piperidinecarboxylate, 73733-86-5.

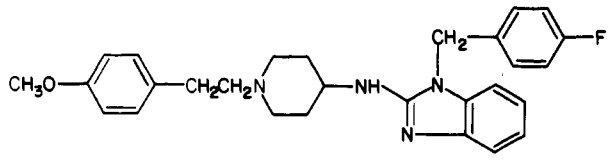
New Antihistaminic N-Heterocyclic 4-Piperidinamines. 3. Synthesis and Antihistaminic Activity of *N*-(4-Piperidinyl)-3*H*-imidazo[4,5-*b*]pyridin-2-amines

Frans Janssens,* Joseph Torremans, Marcel Janssen, Raymond A. Stokbroekx, Marcel Luyckx, and Paul A. J. Janssen

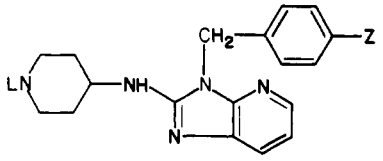
N. V. Janssen Pharmaceutica, Research Laboratories, B-2340 Beerse, Belgium. *Received February 4, 1985*

To study the bioisosteric replacement of a 2-pyridyl ring for a phenyl nucleus in astemizole, a series of *N*-(4-piperidinyl)-3*H*-imidazo[4,5-*b*]pyridin-2-amines was synthesized and evaluated. The title compounds were obtained starting from either **8a** or **8b** by four synthetic methods. The in vivo antihistamine activity was evaluated by the compound 48/80-induced lethality test in rats and the histamine-induced lethality test in guinea pigs after oral and/or subcutaneous administration. Compound **37**, the isostere of astemizole, showed the most potent antihistaminic properties in the rat. However, astemizole is superior to **37** as to duration of action and total potency.

Astemizole, a prototype of a new series of *N*-(4-piperidinyl)-1*H*-benzimidazol-2-amines, is a potent, long-lasting, and selective in vivo antihistamine, not affecting the central nervous system in different animal species, after both oral and subcutaneous administration.[1-3]



astemizole



I, Z = H or F

Replacement of a phenyl nucleus by a 2-pyridyl ring in the structure of various classical H_1-antagonists considerably enhances antihistaminic activity.[4] A series of *N*-(4-piperidinyl)-3*H*-imidazo[4,5-*b*]pyridin-2-amines (I) was synthesized in order to evaluate this well-known bioisosteric replacement[5] in astemizole and related compounds.

Chemistry. In the synthetic approach to the *N*-(4-piperidinyl)-3*H*-imidazo[4,5-*b*]pyridin-2-amines, benzylamine **1** was allowed to react with 2-chloro-3-nitropyridine (**2**) to form **3a,b** (Scheme I). Catalytic reduction of the nitro function of **3a,b** quantitatively yielded **4a,b**, which were immediately coupled with isothiocyanate **5**[1] to yield **6a,b**. Cyclodesulfurization of **6a,b** with mercury oxide in tetrahydrofuran afforded **7a,b**.[1] Deprotection with 48% HBr at reflux gave the intermediates **8a,b** (Table I).

The test compounds **9–39** originated from **8a,b** by one of the following four methods:[1,2] alkylation with LX in dimethylformamide at 70–90 °C (method A); addition of vinylpyridines in butanol (method B); reductive amination of ketones or aldehydes (method C); oxirane cleavage in a benzene–methanol mixture (method D).

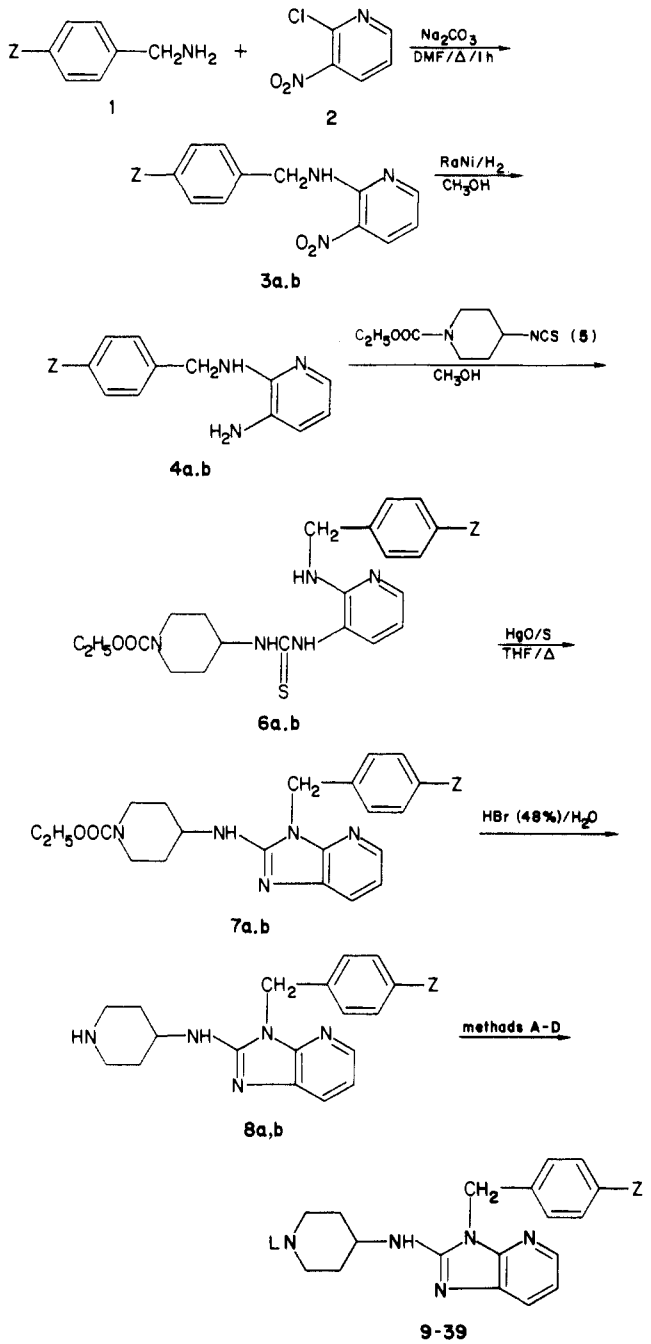
Results and Discussion

The in vivo, antihistamine activity was evaluated by the compound 48/80-induced lethality test in rats;[6] the results

(1) Part 1: Janssens, F.; Torremans, J.; Janssen, M.; Stokbroekx, R. A.; Luyckx, M.; Janssen, P. A. J. *J. Med. Chem.*, first of three papers in this issue.
(2) Part 2: Janssens, F.; Torremans, J.; Janssen, M.; Stokbroekx, R. A.; Luyckx, M.; Janssen, P. A. J. *J. Med. Chem.*, second of three papers in this issue.
(3) Van Wauwe, J.; Awouters, F.; Niemegeers, C. J. E.; Janssens, F.; Van Nueten, J. M.; Janssen, P. A. J. *Arch. Int. Pharmacodyn. Ther.* 1981, *251*, 39.
(4) Casy, A. F. In "Handbook of Experimental Pharmacology"; Rocha, E., Silva, M., Eds.; Springer Verlag: New York, 1978.
(5) Thornber, C. N. *Chem. Soc. Rev.* 1979, *8*, 563 and references cited therein.
(6) Niemegeers, C. J. E.; Awouters, F.; Van Nueten, J. M.; De Nollin, S.; Janssen, P. A. J. *Arch. Int. Pharmacodyn. Ther.* 1978, *234*, 164.
(7) Awouters, F.; Niemegeers, C. J. E.; Janssen, P. A. J. *Drug Dev. Res.* 1981, *1*, 107.

0022-2623/85/1828-1943$01.50/0

Scheme I[a]



[a] Key: a, Z = H; b, Z = F.

are summarized in Table II (oral and subcutaneous administration). The duration of action for antihistamine activity of astemizole was compared with the isosteric compound **37** in the histamine-induced lethality test in guinea pigs[3] (Table III).

Maximal in vivo antihistamine activity after subcutaneous administration in the 48/80 lethality test in the rat is found for **35** and **39**, followed by **9**, **15**, **24** and **29**. Of these, only **24**, **35**, and **39** show moderate oral activity.

The alkyl- or alkenyl-substituted piperidines **9–14** exhibit good to excellent subcutaneous activity but again lack sufficient oral activity. Introduction of an aromatic group, linked to the piperidine nitrogen atom either via an alkyl, alkenyl, alkanoyl, or an alkoxy chain, results in excellent subcutaneous antihistamine activity (**15–21**, **25**, **30–35**, **37**, **39**). Oral effectiveness is good to moderate, except for **15**, **25**, **30**, **31**, **33**, and **34**. Fluoro substitution on the benzyl group does not significantly alter activity as illustrated by the pairs **9-29** (L = Me), **15-30** (L = $C_6H_5CH_2CH_2$), and **16-37** (L = 4-$CH_3OC_6H_4CH_2CH_2$).

As could be expected from our previous results[1,2] the (4-methoxyphenyl)ethyl derivatives **16** and **37** (Z = H, F), and to a lesser extent **32** (a phenoxyethyl derivative) and **35** (a 2-pyridylethyl derivative), exhibit pronounced antihistamine activity after oral administration.

Compared with astemizole, several compounds are subcutaneously more active, but only **37**, the isosteric imidazopyridinamine analogue, appears to be equipotent for oral activity, at least 2 h after administration (Table II). Judged by the histamine lethality test in guinea pigs, **37** and astemizole have an almost comparable duration of action, although that of **37** seems to be somewhat shorter based on the 48-h results (Table III).

In general, it can be concluded that substitution of an imidazo[4,5-*b*]pyridin-2-amine ring for a 2-aminobenzimidazole nucleus slightly reduces oral activity, with a few exceptions, while subcutaneous activity is enhanced, particularly in the benzyl series.[1,2]

Experimental Section

Chemistry. Melting points were determined with a Mettler FP_1 melting point apparatus and are uncorrected. Elemental analyses were performed by the analytical department of Janssen Pharmaceutica Laboratories. Mass spectra were measured with a Varian Matt 311-eV emission spectrometer. NMR spectra were measured with either a Brucker HX 60-12 or a Brucker WP 80-DS instrument (internal standard Me_4Si). UV and IR spectra were determined with a Beckman DK-2A and a Perkin-Elmer 421 or 225 spectrometer. Analytical TLC was performed on silica 60 F_{254} (Merck), and the spots were made visible by a UV lamp or iodine vapor.

***N*-[(4-Fluorophenyl)methyl]-3-nitro-2-pyridinamine (3b).** A suspension of 4-fluorobenzylamine (9.7 g, 0.06 mol), 2-chloro-3-nitropyridine (9.4 g, 0.06 mol),[8] and sodium carbonate (10.6 g, 0.1 mol) in dimethylformamide (100 mL) was stirred for 1 h at 90 °C. The reaction mixture was cooled and poured into water. The solid product was collected and crystallized from 2-propanol to yield **3b**: 10.5 g (71%); mp 74 °C. Anal. ($C_{12}H_{10}FN_3O_2$) C, H, N, F.

Ethyl 4-[[[[2-[[(4-Fluorophenyl)methyl]amino]-3-pyridinyl]amino]thioxomethyl]amino]-1-piperidinecarboxylate (6b). (i) A solution of **3b** (10.5 g, 0.043 mol) in methanol (250 mL) was hydrogenated over RaNi (2 g) at atmospheric pressure and room temperature. After uptake of 3 equiv of hydrogen, the catalyst was filtered off and the filtrate was evaporated, affording *N*²-[(4-fluorophenyl)methyl]-2,3-pyridinamine (**4b**; 9.3g, 100%) (TLC 1 spot).

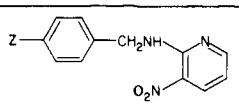
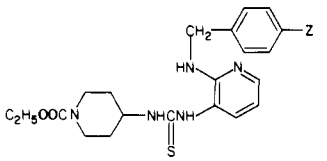
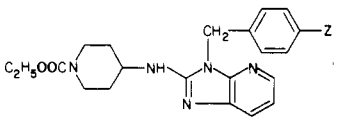
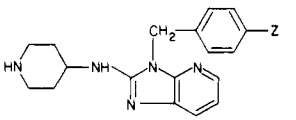
(ii) A solution of ethyl 4-isothiocyanato-1-piperidinecarboxylate (**5**) (9.2 g, 0.043 mol)[1] and **4b** (9.3 g, 0.043 mol) in methanol (300 mL) was stirred and refluxed for 2 h. The solvent was evaporated in vacuo, and the residue was crystallized from 2-propanol to yield **6b**: 10 g (54%); mp 166.5 °C. Anal. ($C_{21}H_{26}FN_5O_2S$) C, H, N, S.

Ethyl 4-[[3-[(4-Fluorophenyl)methyl]-3*H*-imidazo[4,5-*b*]pyridin-2-yl]amino]-1-piperidinecarboxylate (7b). A suspension of **6b** (8.6 g, 0.02 mol), yellow mercury oxide (6.5 g, 0.03 mol), and a catalytic amount of sulfur in tetrahydrofuran (150 mL) was refluxed for 3 h. The solvent was evaporated, and the residue was crystallized from a mixture of 4 methyl-2-pentanone and diisopropyl ether to yield **7b**: 7 g (88%); mp 134.4 °C. Anal. ($C_{21}H_{24}FN_5O_2$) C, H, N, F.

3-[(4-Fluorophenyl)methyl]-*N*-(4-piperidinyl)-3*H*-imidazo[4,5-*b*]pyridin-2-amine Dihydrochloride Monohydrate (8b). A solution of **7b** (40 g, 0.1 mol) in 48% hydrobromic acid solution (700 mL) was stirred and heated at 70 °C for 24 h. After evaporation of the solvent in vacuo, the residue was suspended in aqueous ammonia. The base was extracted with chloroform, dried ($MgSO_4$), and evaporated. The crude base was

(8) Supplied by Aldrich.

Table I

compd	struct	Z	formula	mp, °C	yield[a]	crystn[b] solv	anal.
3a		H	$C_{12}H_{11}N_3O_2$	75[c]	80	A	C, H, N
3b		F	$C_{12}H_{10}FN_3O_2$	74	71	A	C, H, N, F
6a		H	$C_{21}H_{27}N_5O_2S$	146.7	70	B	C, H, N, S
6b		F	$C_{21}H_{26}FN_5O_2S$	166.5	54	A	C, H, N, S
7a		H	$C_{21}H_{25}N_5O_2$	148.6	50	A	C, H, N
7b		F	$C_{21}H_{24}FN_5O_2$	134.4	88	B	C, H, N, F
8a		H	$C_{18}H_{21}N_5 \cdot 2HCl \cdot H_2O$	298.1	14	A	C, H, N, Cl
8b		F	$C_{18}H_{20}FN_5 \cdot 2HCl \cdot H_2O$	269.7	67	A	C, H, N, F

[a] Based on immediate precursor, after recrystallization. Generally no attempts made to optimize yields. [b] A = 2-propanol; B = 4-methyl-2-pentanone. [c] Mp 75 °C.[10]

treated with hydrogen chloride and crystallized from 2-propanol to afford **8b**: 34.2 g (86%); mp 269.7 °C. Anal. ($C_{18}H_{20}FN_5 \cdot 2HCl \cdot H_2O$) C, H, N, F, H_2O.

Method A. 3-[(4-Fluorophenyl)methyl]-*N*-[1-[2-(4-methoxyphenyl)ethyl]-4-piperidinyl]-3*H*-imidazo[4,5-*b*]pyridin-2-amine (37). A suspension of 4-methoxyphenyl ethanolmethanesulfonate ester[1] (2.3 g, 0.01 mol), **8b** (3.25 g, 0.01 mol), and sodium carbonate (1.1 g, 0.01 mol) in dimethylformamide (100 mL) was stirred at 70 °C for 20 h. After cooling, the reaction mixture was poured into water and extracted twice with toluene. The combined organic layers were dried ($MgSO_4$), filtered, and evaporated. Chromatographic purification (eluant chloroform–methanol, 98:2 (v/v)) and crystallization from a solvent mixture of acetone and diisopropyl ether yielded **37**: 1.2 g (26%); mp 149.1 °C. Anal. ($C_{27}H_{30}FN_5O$) C, H, N, F.

Method B. 3-[(4-Fluorophenyl)methyl]-*N*-[1-[2-(2-pyridinyl)ethyl]-4-piperidinyl]-3*H*-imidazo[4,5-*b*]pyridin-2-amine (35). A solution of 2-vinylpyridine (6.3 g, 0.06 mol) and **8b** (10 g, 0.03 mol) in butanol (200 mL) was stirred and refluxed overnight. The solvent was evaporated in vacuo, and the residue was chromatographed on silica (eluant chloroform–methanol 97:3 (v/v)). The pure product was collected and crystallized from a mixture of acetone and diisopropyl ether to yield **35**: 4.8 g (37%); mp 157.1 °C. Anal. ($C_{25}H_{27}FN_6$) C, H, N, F.

Method C. *N*-[1-(1-Methylethyl)-4-piperidinyl]-3-(phenylmethyl)-3*H*-imidazo[4,5-*b*]pyridin-2-amine (10). A solution of acetone (10 mL), **8a**·2HCl (3.8 g, 0.01 mol),[9] and sodium acetate (4 g, 0.05 mol) in methanol (100 mL) was hydrogenated over Pd/C 10% (2 g) at normal pressure and at 25 °C. The catalyst was filtered off after uptake of 1 equiv of hydrogen, and the filtrate was evaporated. The residue was treated with water, alkalized with sodium hydroxide, and extracted with chloroform. The combined organic layers were dried ($MgSO_4$), filtered, and evaporated. Recrystallization from a mixture of methanol and diisopropyl ether afforded **10**: 1.4 g (40%); mp 136.4 °C. Anal. ($C_{21}H_{27}N_5$) C, H, N.

Method D. α-(Phenoxymethyl)-4-[[3-(phenylmethyl)-3*H*-imidazo[4,5-*b*]pyridin-2-yl]amino]-1-piperidineethanol (20). A suspension of (phenoxymethyl)oxirane (3 g, 0.02 mol)[8], **8a**·2HCl (3.8 g, 0.01 mol), and sodium carbonate (2.1 g, 0.02 mol) in benzene (150 mL) and methanol (50 mL) was stirred and refluxed overnight. The solvents were evaporated, and the residue was recrystallized from 2-propanol to yield **20**: 1.6 g (35%); mp 136.6 °C. Anal. ($C_{27}H_{31}N_5O_2$) C, H, N.

Pharmacological Methods. The in vivo potency and duration were determined in rats and guinea pigs as described previously.[3,6]

Protection of rats from compound 48/80-induced lethality: Compound 48/80, a mixture of oligomers obtained by condensation of 4-methoxy-*N*-methylbenzeneethanamine and formaldehyde has been described as a potent histamine-releasing agent in rats.[7] The protection from compound 48/80-induced lethal circulatory collapse appears to be a simple way of evaluating quantitatively the antihistaminic activity of test compounds. Male rats of an inbred Wistar strain, weighing 230–270 g, were used in the experiment. After overnight starvation the rats were transferred to conditioned laboratories (temperature 21 ± 1 °C, relative humidity 65 ± 5%).

The rats were treated subcutaneously or orally with a test compound or with the solvent (NaCl solution, 0.9%). One hour after treatment there was injected intravenously compound 48/80, freshly dissolved in water, at a dose of 0.5 mg/kg (0.2 mL/100 g of body weight). In control experiments, wherein 250 solvent-treated animals were injected with the standard dose of compound 48/80, not more than 2.8% of the animals survived after 4 h. Survival after 4 h is therefore considered to be a safe criterion of a protective effect of drug administration. Calculated ED_{50} values with confidence limits, according to Finney,[11] were obtained on the basis of test results on five animals for each of at least three doses from the geometrical series 0.0025, 0.005, 0.01, ..., 10.0, 20.0, and 40.0 mg/kg. Estimated ED_{50} values, after oral (−2 h) and/or subcutaneous (−1 h) administration, were based on at least two animals per test dose.

Protection of Guinea Pigs from Histamine-Induced Lethality. The 50% protective dose (PD_{50}) values against a lethal intravenous dose of histamine was determined by the following method: Male albino guinea pigs (280–360 g) were challenged with an intravenous injection of 1.25 mg/kg of histamine dihydrochloride. As all control animals died within 5 min, survival after 1 h was considered to be a safe criterion of protection from histamine-induced death. To study the duration of action, twofold increments of the test substance were administered orally 3, 24, 48, and 96 h prior to intravenous histamine challenge.

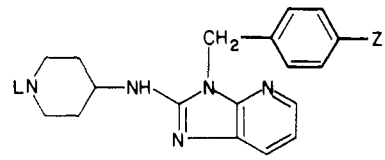
PD_{50} values with confidence limits were computed according to Finney.[11] Four to six guinea pigs per dose and time point were used for each of at least three doses from the geometrical series 0.0025, 0.005, 0.01, ..., 2.5, and 5.0 mg/kg. Estimated PD_{50} values were based on at least two animals per test dose.

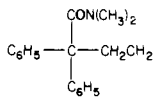
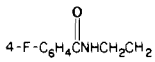
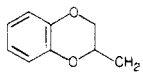
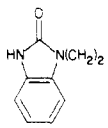
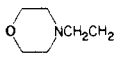
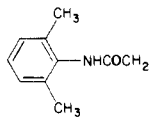
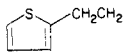
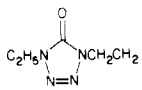
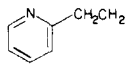
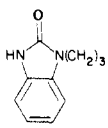
(9) Prepared analogously to **8b**. For analytical results see Table I.

(10) Grube, H.; Suhr, H. *Chem. Ber.* **1969**, *102*, 1570.

(11) Finney, D. J. "Probit Analysis"; University Press: Cambridge, 1962.

Table II



compd	L	Z	formula	mp, °C	yield,[a] %	crystn solv[b]	anal.	method	compd 48/80 leth test in rats:[c] ED_{50}, mg/kg −1 h sc	−2 h oral
9	CH_3	H	$C_{19}H_{23}N_5$	141.4	50	E	C, H, N	C	0.08	>2.5
10	i-C_3H_7	H	$C_{21}H_{27}N_5$	136.4	40	C-E	C, H, N	C	0.63	>2.5
11	n-C_4H_9	H	$C_{22}H_{29}N_5$	147.5	41	C-E	C, H, N	A	0.16	>2.5
12	n-C_6H_{13}	H	$C_{24}H_{33}N_5$	137.3	68	E	C, H, N	A	0.16	2.5
13		H	$C_{24}H_{31}N_5$	129.2	31	C-E	C, H, N	C	0.63	>2.5
14	CH_2=$CHCH_2$	H	$C_{21}H_{25}N_5$	132.6	29	C-E	C, H, N	A	0.31	>2.5
15	$C_6H_5CH_2CH_2$	H	$C_{26}H_{29}N_5$	153.2	54	A-E	C, H, N	A	0.08	>2.5
16	4-$CH_3OC_6H_4$-CH_2CH_2	H	$C_{27}H_{31}N_5O$	124.1	45	E	C, H, N	A	0.16	0.31
17	C_6H_5CH=$CHCH_2$	H	$C_{27}H_{29}N_5$	124.6	52	C-E	C, H, N	A	1.25	1.25
18	$C_6H_5OCH_2CH_2$	H	$C_{26}H_{29}N_5O$	142.5	23	C-E	C, H, N	A	0.31	1.25
19	4-$FC_6H_4O(CH_2)_3$	H	$C_{27}H_{30}FN_5O$	124.9	43	C-E	C, H, N, F	A	1.25	1.25
20	$C_6H_5OCH_2CH(OH)CH_2$	H	$C_{27}H_{31}N_5O_2$	136.6	35	A	C, H, N	D	0.16	0.63
21	4-$FC_6H_4C(O)(CH_2)_3$	H	$C_{28}H_{30}FN_5O$	141.0	30	C-E	C, H, N, F	A	0.31	1.25
22		H	$C_{36}H_{40}N_6O$	193.4	61	C-E	C, H, N	A	>2.5	nt
23	$(C_6H_5)_2CHCH_2CH_2$	H	$C_{33}H_{35}N_5$	141.4	26	C-E	C, H, N	C	>2.5	nt
24		H	$C_{27}H_{29}FN_6O$	187.5	42	D	C, H, N	A	0.08	1.25
25		H	$C_{27}H_{29}N_5O_2$	184.7	18	C-E	C, H, N	A	0.63	>2.5
26		H	$C_{28}H_{31}N_7O$	221.7	46	A-E	C, H, N	A	1.25	1.25
27		H	$C_{24}H_{32}N_6O{\cdot}0.5H_2O$	153.3	24	C-E	C, H, N	A	0.63	2.5
28		H	$C_{28}H_{32}N_6O$	176.8	47	C-E	C, H, N	A	>2.5	nt
29	CH_3	F	$C_{19}H_{22}FN_5$	154.4	24	A	C, H, N, F	C	0.08	>2.5
30	$C_6H_5CH_2CH_2$	F	$C_{26}H_{26}FN_5$	193.2	47	A	C, H, N, F	A	0.31	>2.5
31	C_6H_5CH=$CHCH_2$	F	$C_{27}H_{28}FN_5$	152.8	20	E	C, H, N	A	1.25	>2.5
32	$C_6H_5OCH_2CH_2CH_2$	F	$C_{27}H_{30}FN_5O$	157.6	30	D-E	C, H, N	A	0.31	0.31
33		F	$C_{24}H_{26}FN_5S$	176.2	30	D-E	C, H, N, F, S	A	0.16	>2.5
34		F	$C_{23}H_{28}FN_9O$	143.4	26	A-E	C, H, N, F	A	0.31	>2.5
35		F	$C_{25}H_{27}FN_6$	157.2	37	D-E	C, H, N, F	B	0.04	0.31
36		F	$C_{28}H_{30}FN_7O$	202.4	46	D	C, H, N, F	A	0.63	2.5
37	4-$CH_3OC_6H_4$-CH_2CH_2	F	$C_{27}H_{30}FN_5O$	149.1	26	D-E	C, H, N, F	A	0.31	0.16
38	$(4\text{-}FC_6H_4)_2CH(CH_2)_3$	F	$C_{34}H_{34}F_3N_5$	131.9	18	C-E	C, H, N, F	A	>2.5	nt
39	4-$FC_6H_4C(O)(CH_2)_3$ astemizole	F	$C_{28}H_{29}F_2N_5O$	161.5	10	C-E	C, H, N, F	A	0.04 0.11[d] (0.08–0.16)	1.25 0.11[d] (0.076–0.16)

[a] Based on immediate precursor, after recrystallization. Generally no attempts made to optimize yields. [b] A = 2-propanol; B = 4-methyl-2-pentanone; C = methanol; D = acetone; E = diisopropyl ether. [c] The estimated ED_{50} are used whenever possible. For inactive compounds the highest dose tested is indicated preceded by the symbol > (greater than). Compounds that are not tested are designated nt. [d] Confidence limits.

Table III. Protection from Intravenous Histamine Lethality in Guinea Pigs

compd	ED_{50}, mg/kg: hours after oral administrn			
	3	24	48	96
37	0.16	0.12	0.25	nt[a]
astemizole	0.33 (0.25–0.43)[b]	0.07 (0.05–0.09)[b]	0.04 (0.03–0.07)[b]	0.19 (0.10–0.35)[b]

[a] Not tested = nt. [b] Confidence limits.

Acknowledgment. The authors thank the "Instituut tot aanmoediging van het Wetenschappelijk Onderzoek in Nijverheid en Landbouw" for financial support. The authors thank Dr. R. Boar for helpful discussions and S. Daniels for typing the manuscript.

Registry No. **1a**, 100-46-9; **2**, 140-75-0; **3**, 5470-18-8; **3a**, 3723-70-4; **3b**, 73733-74-1; **4a**, 32282-07-8; **4b**, 73733-75-2; **5**, 73733-70-7; **6a**, 73733-83-2; **6b**, 75971-36-7; **7a**, 73734-02-8; **7b**, 73733-99-0; **8a**, 76031-50-0; **8a**·2HCl, 73734-21-1; **8b**, 75979-00-9; **8b**·2HCl, 73734-27-7; **9**, 73735-95-2; **10**, 73736-00-2; **11**, 73735-17-8; **12**, 73735-27-0; **13**, 73735-99-6; **14**, 73735-22-5; **15**, 73735-12-3; **16**, 75970-98-8; **17**, 73735-25-8; **18**, 73735-18-9; **19**, 73755-86-9; **20**, 75971-13-0; **21**, 73735-26-9; **22**, 98331-30-7; **23**, 73735-19-0; **24**, 73735-74-7; **25**, 73735-21-4; **26**, 98331-31-8; **27**, 73735-24-7; **28**, 98331-32-9; **29**, 73735-94-1; **30**, 73734-48-2; **31**, 73734-78-8; **32**, 73734-60-8; **33**, 73735-68-9; **34**, 73735-00-9; **35**, 73735-72-5; **36**, 73735-33-8; **37**, 73755-88-1; **38**, 98331-33-0; **39**, 73755-85-8; 4-methoxyphenylethanol methanesulfonate (ester), 73735-36-1; 2-vinylpyridine, 100-69-6; acetone, 67-64-1; acetaldehyde, 75-07-0; cyclohexanecarboxaldehyde, 2043-61-0; butanaldehyde, 123-72-8; (phenoxymethyl)oxirane, 122-60-1.

Notes

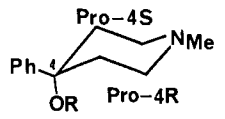
Racemic and Optically Active 1,3,3-Trimethyl-4-phenyl-4-(propionyloxy)piperidine

F. R. Ahmed,[†] G. F. Laws,[‡] A. E. Madani,[§] and A. F. Casy*

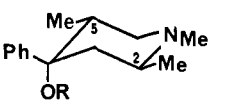
School of Pharmacy and Pharmacology, University of Bath, Claverton Down, Bath BA2 7AY, U.K., and Division of Biological Sciences, National Research Council of Canada, Ottawa K1A 0R6, Canada. *Received August 15, 1984*

The preparation and resolution of 1,3,3-trimethyl-4-phenyl-4-(propionyloxy)piperidine (**5**, 3-methylprodine) are described, and the results of the antinociceptive activities of the products by hot-plate (mice) and tail-withdrawal (rats) tests are shown to support proposals made from a recent analysis of the stereochemical structure–activity relationships of *C*-methyl derivatives of the reversed ester of meperidine. Data of absolute configuration were obtained by X-ray crystallography of a hydrobromide salt.

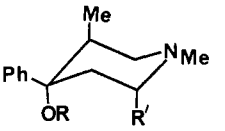
The effect of alkyl substitution in the piperidine ring of 4-phenylpiperidine analgesics has attracted much interest ever since the 3-methyl analogues of the reversed ester of meperidine were described in the late 1940s.[1] Since that time many 3-alkyl and all possible mono- and nongeminal di-*C*-methyl derivatives of the reversed ester have been reported, and much data have accrued on potency variations among isomeric sets and their relative and absolute geometries. In a recent analysis of these results[2] a consistent stereochemical structure–activity pattern was developed on the basis of 4-phenylpiperidine ligands associating with the opiate receptor in the form of equatorial 4-phenyl chair conformations. Thus, the fact of the preferred placement of methyl α and β to nitrogen in the Pro-4*R* and Pro-4*S* edges respectively of the unsubstituted reversed ester **1**[3,4] is consistent with the absolute stereochemistry of the more active γ-2,5-dimethyl analogue (*d*-γ-promedol (**2**))[5] and the inactivities of the β-2,3-dimethyl (either antipode must present one unfavorably positioned substituent) and *cis*-2,6- and *cis*-3,5-dimethyl analogues.[6,7] The same steric correlation obtains between the more active antipodal forms of β-prodine (**3**, R′ = H) and α-promedol (**3**, R′ = Me).[3,8] These and other results of stereochemical analyses of *C*-methyl reversed esters of meperidine allow the absolute orientations of methyl



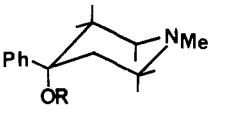
1, R = COEt throughout



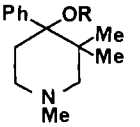
2



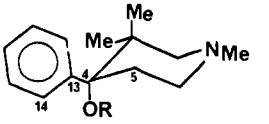
3



4 (solid lines denote positions of permitted Me substitution)



5



6 (4*R* isomer)

[†] National Research Council of Canada.

[‡] Visitor from Department of Pharmacy, University of Otago Medical School, Dunedin, New Zealand.

[§] Visitor from College of Pharmacy, King Saud University, Riyadh, Saudi Arabia.

(1) Randall, L. O.; Lehman, G. *J. Pharmacol. Exp. Ther.* **1948**, *93*, 314.

0022-2623/85/1828-1947$01.50/0