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Compounds Related to Pethidine—II. Mannich Bases Derived from Various Esters of 4-Carboxy-4-phenylpiperidine and Acetophenones

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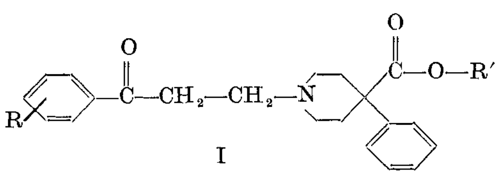
Introduction

In a previous paper[1] some physical and pharmacological properties of a series of 3-{1-[4′-carbethoxy-4′-phenyl]piperidino} propiophenones (I: $R' = C_2H_5$) were described.

The purpose of this second part is to present a series of 29 related esters (I) and to compare their pharmacological properties.



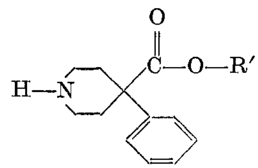
I

These compounds are of general formula (I) in which R is a substituent such as alkyl, hydroxyl and halogen, and R′ an unsubstituted alkyl- or aralkyl-group other than ethyl.

Preparation of the compounds

The compounds were obtained by one of the methods of condensation mentioned in Part I,[1] using the appropriate ester.

The intermediate esters of 4-carboxy-4-phenylpiperidine (II)



II

were prepared by the procedure described by Eisleb;[2] the analytical data are reported in Table I.

Table I. Analytical data for the intermediate norpethidine-like esters (II)

	R′	Formula	m.p. (b.p.) °C	Equivalent weight Calcd.	Equivalent weight Found	Halogen % Calcd.	Halogen % Found
1	CH_3	$C_{13}H_{17}NO_2$ base [(a)]	(b_3 145)	219	222	—	—
2	CH_3	$C_{13}H_{17}NO_2$ HBr	230·5–1·5	300	306	26·62	26·37
3	CH_3	$C_{13}H_{17}NO_2$ HCl	209·5–12	256	255	13·86	13·53
4	C_2H_5	$C_{15}H_{19}NO_2$ HCl	108·8–9·4	282	277	12·58	12·40
5	n-C_3H_7	$C_{15}H_{21}NO_2$ base	(b_8 180)	247	247	—	—
6	n-C_3H_7	$C_{15}H_{21}NO_2$ HBr	103·6–4·2	328	326	24·35	22·50
7	n-C_3H_7	$C_{15}H_{21}NO_2$ HCl	93·6–4	284	275	12·49	11·91
8	*iso*-C_3H_7	$C_{15}H_{21}NO_2$ base [(b)]	(b_6 174)	247	243	—	—
9	*iso*-C_3H_7	$C_{15}H_{21}NO_2$ HCl	68–9·5	284	263	12·49	15·22
10	n-C_4H_9	$C_{16}H_{23}NO_2$ base [(c)]	(b_2 165)	261	260	—	—
11	n-C_4H_9	$C_{16}H_{23}NO_2$ HCl	112–3	298	293	11·91	11·80
12	sec-C_4H_9	$C_{18}H_{23}NO_2$ HCl	99–105	298	309	11·91	11·95
13	n-C_5H_{11}	$C_{17}H_{25}NO_2$ base [(d)]	(b_2 174–6)	275	263	—	—
14	n-C_6H_{13}	$C_{18}H_{27}NO_2$ base [(e)]	(b_1 175–80)	289	271	—	—
15	C_6H_{11}	$C_{18}H_{25}NO_2$ HBr	185–6	368	371	21·70	21·76
16	C_6H_{11}	$C_{18}H_{25}NO_2$ HCl	244–5·5	324	323	10·95	10·58
17	n-C_7H_{15}	$C_{19}H_{29}NO_2$ base [(f)]	(b_1 183)	303	283	—	—
18	$CH_2CH_2C_6H_5$	$C_{20}H_{23}NO_2$ HCl	161–3	346	345	10·25	9·79

(a) n_D^{20}: 1·5433; d_4^{20}: 1·139 (b) n_D^{20}: 1·5203; d_4^{20}: 1·057 (c) n_D^{20}: 1·5221; d_4^{20}: 1·083

(d) n_D^{20}: 1·5154; d_4^{20}: 1·025 (e) n_D^{20}: 1·5117; d_4^{20}: 1·0205 (f) n_D^{20}: 1·5061; d_4^{20}: 1·021

The following preparation is illustrative of the general procedure.

Table II. Analytical data of the propiophenones (I)

Serial number		R	R′	Formula	m.p. °C	Equiv. weight		Halogen %		U.V. max.	
						Calcd.	Found	Calcd.	Found	mμ	ε.10⁻³
1	R 993	H	CH_3	$C_{22}H_{25}NO_3$ HCl	189·2–91·5	388	388	9·14	8·96	242	13·3
2	R 1404	H	C_3H_5	$C_{24}H_{27}NO_3$ HCl	182–3	414	416	8·57	8·61	245	13·4
3	R 1007	H	*n*-C_3H_7	$C_{24}H_{29}NO_3$ HCl	172–3	416	416	8·52	8·64	247	13·2
4	R 1041	H	*iso*-C_3H_7	$C_{24}H_{29}NO_3$ HCl	177–8·6	416	413	8·52	8·36	243	13·2
5	R 1262	H	*n*-C_4H_9	$C_{25}H_{31}NO_3$ HCl	164·2–4·8	430	427	8·25	8·41	244	14·4
6	R 1298	H	*sec*-C_4H_9	$C_{25}H_{31}NO_3$ HCl	155–6·2	430	431	8·25	8·33	—	—
7	R 1367	H	*n*-C_5H_{11}	$C_{26}H_{33}NO_3$ HCl	156·2–7·4	444	440	7·99	7·99	245	14·2
8	R 1494	H	*n*-C_6H_{13}	$C_{27}H_{35}NO_3$ HCl	146·6–8·8	458	462	7·74	7·71	245	13·4
9	R 1361	H	C_6H_{11}	$C_{27}H_{33}NO_3$ HCl	155–6·2	456	454	7·78	7·65	244	14·2
10	R 1488	H	*n*-C_7H_{15}	$C_{28}H_{37}NO_3$ HCl	146–7·5	472	472	7·51	7·48	245	12·3
11	R 1373	H	CH_2-CH_2-C_6H_5	$C_{29}H_{31}NO_3$ HCl	176·8–7·2	478	478	7·42	7·35	245	14·4
12	R 2036	4-F	CH_3	$C_{22}H_{24}FNO_3$ HCl	204–5	406	400	8·73	8·80	249	11·7
13	R 2100	4-F	*iso*-C_3H_7	$C_{24}H_{28}FNO_3$ HCl	183·8–4·6	434	433	8·17	8·32	248	11·9
14	R 1447	3-Br	CH_3	$C_{22}H_{24}BrNO_3$ HCl	215–6	467	475	7·60	7·75	245	10·1
15	R 1450	3-Br	*iso*-C_3H_7	$C_{24}H_{28}BrNO_3$ HCl	174·6–6·8	494	494	7·16	7·29	246	10·1
16	R 1227	4-CH_3	CH_3	$C_{23}H_{27}NO_3$ HCl	195·2–5·8	402	410	8·82	9·01	256	16·5
17	R 1233	4-CH_3	*n*-C_3H_7	$C_{25}H_{31}NO_3$ HCl	165·5–6·5	430	426	8·25	8·30	257	16·1
18	R 1217	4-CH_3	*iso*-C_3H_7	$C_{25}H_{31}NO_3$ HCl	189–90	430	422	8·35	8·35	255	15·9
19	R 1307	4-CH_3	*n*-C_4H_9	$C_{26}H_{33}NO_3$ HCl	148–9	444	443	7·99	7·96	256	16·0
20	R 1444	2,5-$(CH_3)_2$	CH_3	$C_{24}H_{29}NO_3$ HCl	185–7·5	416	417	8·52	8·58	250	9·8
21	R 1453	2,5-$(CH_3)_2$	*iso*-C_3H_7	$C_{26}H_{33}NO_3$ HCl	163·2–5·4	444	450	7·99	7·97	249	9·5
22	R 1446	4-C_2H_5	CH_3	$C_{24}H_{29}NO_3$ HCl	195·4–7	416	414	8·52	8·56	256	16·9
23	R 1478	4-C_2H_5	*iso*-C_3H_7	$C_{26}H_{33}NO_3$ HCl	147·8–8·8	444	452	7·99	8·25	258	17·0
24	R 1001	2-OH	CH_3	$C_{22}H_{25}NO_4$ HCl	198–9·5	404	399	8·78	8·52	252	10·2
25	R 1257	2-OH	*n*-C_3H_7	$C_{24}H_{29}NO_4$ HCl	150–1	432	432	8·21	8·08	254	11·2
26	R 1292	2-OH	*iso*-C_3H_7	$C_{24}H_{29}NO_4$ HCl	151–2	432	433	8·21	8·03	254	10·5
27	R 1278	2-OH	*n*-C_4H_9	$C_{25}H_{31}NO_4$ HCl	162–3	446	447	7·95	7·98	255	10·8
28	R 1443	4-OCH_3	CH_3	$C_{23}H_{27}NO_4$ HCl	206–8	418	418	8·50	8·53	279	17·1
29	R 1451	4-OCH_3	*iso*-C_3H_7	$C_{25}H_{31}NO_4$ HCl	167·8–70·8	446	445	7·95	7·97	281	16·2

Preparation of 4-Carbobutoxy-4-phenylpiperidine (*II: R′* = *n* = C_4H_9)

A solution of 170 g (0·5 M) of *N*-tosyl-4-phenyl-4-cyanopiperidine[2] in 230 g of 75 per cent sulphuric acid was made, with stirring and heating at 140–150°. The heating was continued for 3 h. After cooling to 110°, the reflux condenser was replaced to allow distillation and 2 l. *n*-butanol added to the mixture drop-wise over a period of 3 h. The reflux condenser was then re-inserted and the mixture refluxed for another 4 h. Stirring was continued throughout the whole operation. After cooling to room temperature the solution was diluted with 1 l. of distilled water carefully made alkaline with 2 N NaOH and the mixture extracted 4 times with 500 ml of benzene and twice with 200 ml of ether. The organic layers were collected, dried (potassium carbonate), the solvent evaporated and the residual oil fractionated *in vacuo* $b_{1.5}$: 163°. Yield 76 g (58 per cent).

The hydrochlorides are obtained by dissolving the free bases, before or after distillation, in ether and passing dry HCl gas through the solution. The crude salts are filtered and re-crystallized from an appropriate solvent (e.g. *iso*propanol). Analytical data are recorded in Table I.

The propiophenones (I) and their analytical results are listed in Table II.

Pharmacological Methods and Results

The pharmacological methods were described in Part I.[1] The results for the compounds of Table II are recorded in Table III. The following symbols are used: L.L. and U.L.: lower and upper fiducial (confidence) limits ($P = 0\cdot05$); S: slope; f_s: factor for computing confidence limits ($P = 0\cdot05$).

Table III. Pharmacological Results

	Serial number	Test[a]	ED50 mg/kg	L.L.[b]	U.L.[b]	S[b]	f_s[b]	Number of animals
1	R 993	A.M.	0·93	0·78	1·1	1·4	1·1	80
		A.M.	2·1	1·1	4·0	2·1	1·9	80
		A.R.	1·1	0·94	1·2	1·3	1·1	60
		CH	5·3	3·7	7·6	2·5	1·9	50

Table III. Pharmacological Results—*cont.*

	Serial number	Test[a]	ED50 mg/kg	L.L.[b]	U.L.[b]	S[b]	f_s[b]	Number of animals
2	R1404	A.M.	3·4	3·1	3·8	1·6	1·1	170
		M.M.	11	8·4	15	2·0	1·6	170
3	R1007	A.M.	25	22	29	1·5	1·1	85
		M.M.	41	33	51	1·7	1·2	85
		CH	37	30	45	1·4	1·3	30
4	R1041	A.M.	2·3	2·0	2·6	1·6	1·1	140
		M.M.	3·7	3·3	4·2	1·4	1·1	140
		A.R.	3·8	2·8	5·2	2·0	1·5	50
		CH	16	13	18	1·3	1·1	37
5	R1262	A.M.	> 80	—	—	—	—	20
		M.M.	> 80	—	—	—	—	25
6	R1298	A.M.	12	7·2	19	2·1	1·6	65
		M.M.	13	9·0	19	2·8	1·6	65
7	R1367	A.M.	9·2	7·7	11	2·5	1·3	245
		M.M	28	19	40	1·6	1·2	245
8	R1494	A.M.	> 80	—	—	—	—	20
		M.M.	> 80	—	—	—	—	20
		CH	21	14	32	2·7	2·2	50
9	R1361	A.M.	> 80	—	—	—	—	15
		M.M.	> 80	—	—	—	—	15
10	R1488	A.M.	> 80	—	—	—	—	20
		M.M.	> 80	—	—	—	—	20
		CH	21	16	28	1·8	1·4	39
11	R1373	A.M.	> 80	—	—	—	—	25
		M.M.	> 80	—	—	—	—	25
12	R2036	A.M.	5·4	4·2	7·0	1·5	1·1	70
		M.M.	11	7·9	15	2·2	1·3	70
13	R2100	A.M.	37	21	67	3·1	2·6	40
		M.M.	> 80	—	—	—	—	40
14	R1447	A.M.	19	13	27	7·6	1·8	260
		M.M.	> 80	—	—	—	—	260
15	R1450	A.M.	103	73	145	2·4	1·8	75
		M.M.	> 80	—	—	—	—	75
16	R1227	A.M.	5·6	4·8	6·7	1·5	1·2	75
		M.M.	> 10	—	—	—	—	75
17	R1233	A.M.	> 80	—	—	—	—	25
		M.M.	> 80	—	—	—	—	25
		CH	11	7·0	18	2·1	1·7	40
18	R1217	A.M.	22	16	30	2·6	1·8	75
		M.M.	> 50	—	—	—	—	75

Table III. Pharmacological Results—*cont.*

	Serial number	Test[a]	ED50 mg/kg	L.L.[b]	U.L.[b]	S[b]	f_s[b]	Number of animals
19	R1307	A.M.	> 80	64	156	2·3	2·0	35
		M.M.	> 80	—	—	—	—	35
20	R1444	A.M.	72	45	115	2·2	1·7	40
		M.M.	> 80	—	—	—	—	40
21	R1453	A.M.	> 80	—	—	—	—	15
		M.M.	> 80	—	—	—	—	15
22	R1446	A.M.	86	74	101	1·7	1·4	90
		M.M.	> 80	—	—	—	—	90
23	R1478	A.M.	56	45	71	1·5	1·2	35
		M.M.	> 80	—	—	—	—	35
24	R1001	A.M.	4·4	3·8	5·1	1·5	1·2	80
		M.M.	5·8	5·0	6·8	1·5	1·2	80
		A.R.	3·9	3·1	4·9	2·3	1·5	90
		CH	16	8·9	27	4·2	3·0	50
25	R1257	A.M.	> 80	—	—	—	—	25
		M.M.	> 80	—	—	—	—	25
26	R1292	A.M.	12	10	15	3·1	1·3	365
		M.M.	> 40	—	—	—	—	365
27	R1278	A.M.	> 80	—	—	—	—	10
		M.M.	> 80	—	—	—	—	10
28	R1443	A.M.	15	13	17	1·5	1·2	110
		M.M.	> 25	—	—	—	—	110
29	R1451	A.M.	66	47	94	2·2	1·7	60
		M.M.	> 80	—	—	—	—	60

[a] A.M. analgesic activity in mice (S.C.)
M.M. mydriatic activity in mice (S.C.)
A.R. analgesic activity in rats (S.C.)
CH charcoal meal test in mice (I.P.)
[b] For definition see page 312.

Discussion

Analgesic and Mydriatic Activity in Mice

Unsubstituted compounds ($I : R = H$). Table IV shows the unsubstituted compounds (I : R = H) arranged in decreasing order or analgesic effectiveness (ED50 values in μmol/kg) in mice. The results are compared with the corresponding values for serial number R951 (I : R = H; $R' = C_2H_5$). The corresponding mydriatic activities are also shown.

Table IV. Pharmacological results on unsubstituted compounds I (R = H)

Serial number	R′	A.M. ED50 (μmol/kg)	M.M. ED50 (μmol/kg)
R 951	C_2H_5	1·1	1·9
R 993	CH_3	2·6	6·0
R 1041	*iso*-C_3H_7	6·1	9·7
R 1404	CH_2-$CH=CH_2$	9·0	29
R 1367	*n*-C_5H_{11}	23	69
R 1298	*sec*-C_4H_9	30	33
R 1007	*n*-C_3H_7	66	109
R 1494	*n*-C_6H_{13}	> 180	> 180
R 1488	*n*-C_7H_{15}	> 180	> 180
R 1262	*n*-C_4H_9	> 180	> 180
R 1361	C_6H_{11}	> 180	> 180
R 1373	$CH_2CH_2C_6H_5$	> 180	> 180

(1) For the compounds tested, shortening, lengthening, unsaturation, cyclization, or aryl substitution of the ethyl group in the ester function results in a decrease of the analgesic and mydriatic potency in mice.

(2) The decrease of the analgesic and mydriatic activities proceeds in the same order (with one minor exception for R′ = *n*-C_5H_{11}).

(3) The activity of a compound having a branched alkyl group in the ester function is at least 6 times greater than that of the corresponding non-branched homologue.

(4) No simple relation exists between the number of methylene groups in the unbranched alkyl radical R′ and analgesic or mydriatic activity.

Substituted compounds I ($R \neq H$). In view of the fact that predictable pharmacological effects might result from simultaneous modification of R and R′ in I, the analgesic potencies of the most active esters of this series were compared with the corresponding ethyl esters discussed in Part I (Table V).

As indicated by the similarity of the three activity orders of Table V, the influence of the listed R substituents on the analgesic

Table V. Analgesic potency (ED50 in μmol/kg) and activity order of certain esters of type I

R'	R' = Methyl		R' = Ethyl		R' = *iso*Propyl	
	ED50	activity order	ED50	activity order	ED50	activity order
H	2·3	1	1·1	1	5·4	1
2-OH	11	2	2·1	2	28	2
4-F	13	3	2·6	3	85	4
4-CH_3	14	4	8·0	4	51	3
4-OCH_3	35	5	28	6	145	6
3-Br	41	6	12	5	> 180	7½
4-C_2H_5	> 180	7½	100	8	127	5
2,5-$(CH_3)_2$	> 180	7½	75	7	> 180	7½

activity of methyl-, ethyl- and *iso*propyl-esters of structure I is almost independent of the nature of the ester function.

The order of the mydriatic activities in mice of these methyl-, ethyl-, and *iso*propyl esters are recorded in Table VI.

Table VI. Mydriatic activity in mice (ED50: μmol/kg) and activity order

R	R' = Methyl		R' = Ethyl		R' = *iso*-Propyl	
	M.M.	activity order	M.M.	activity order	M.M.	activity order
H	2·1	1	1·9	1	3·7	1
2-OH	14	2	2·9	2	93	2
4-CH_3	25	3	9·6	3	117	3
4-F	27	4	11	4	> 180	6
3-Br	> 180	7	20	5	> 180	6
4-OCH_3	60	5	69	6	> 180	6
2-C_2H_5	> 180	7	> 180	7½	> 180	6
2,5-$(CH_3)_2$	> 180	7	> 180	7½	> 180	6

The correlation between analgesic and mydriatic activity is satisfactory for the more active analgesics and rather poor for the less active ones.

Generally speaking, the following order of decreasing analgesic and mydriatic activity, as found in the various esters discussed in this paper, seems to be quite independent of the nature of substituent R:

$$C_2H_5 > CH_3 > iso\text{-}C_3H_7 > \text{ others.}$$

Analgesic Activity in Rats (A.R.)

Only 5 compounds out of 29 have been tested for analgesic activity in rats. The results may be correlated quite well with those obtained in mice.

Antiperistaltic Activity in Mice (CH)

As shown in Part I, correlation between the analgesic activity and the activity in the charcoal meal test is rather poor (see Table III).

Summary. Some pharmacological properties of a series of 29 Mannich bases derived from various norpethidine-like esters and acetophenones are described.

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