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Compounds Related to Pethidine—IV. New General Chemical Methods of Increasing the Analgesic Activity of Pethidine

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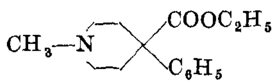
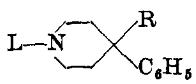
Introduction

A variety of chemical methods are available to increase the analgesic activity of pethidine (I). Replacement of the carbethoxy group ($COOC_2H_5$) by propionoxy ($OCOC_2H_5$) is one of the known methods.[2–6,8,11–13,16,19,20,23–25] Another one is the replacement of N–CH_3 by selected N-substituents such as aralkyl,[2,4,5,17,18,22] propiophenone,[9,10] large alkyl groups,[21] morpholinoethyl,[1,7,14] alkoxy- or phenoxyalkyl.[6,15] The available evidence, on the other hand, seems to indicate that activity usually decreases when carbethoxy ($COOC_2H_5$) is replaced by carbomethoxy ($COOCH_3$), or when propionoxy ($OCOC_2H_5$) is replaced by acetoxy ($OCOCH_3$).[2,4,5,12,23,24,25] (Also unpublished results.)

The purpose of this study is to present new experimental evidence in this field and to arrive at certain tentative generalizations concerning the structure-activity problem of compounds (II) related to pethidine.



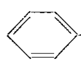
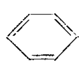
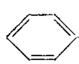
(I)

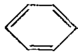
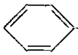
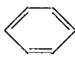
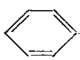
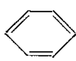
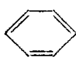


(II)

R = $COOCH_3$, $COOC_2H_5$, $OCOCH_3$, $OCOC_2H_5$.

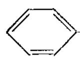
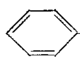
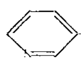
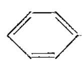
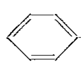
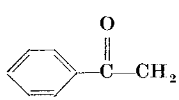
Table I. Analgesic activity of compounds related to pethidine.

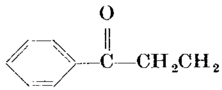
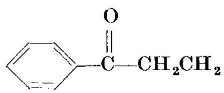
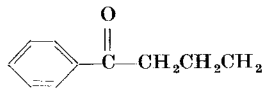
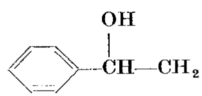
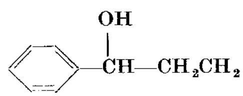
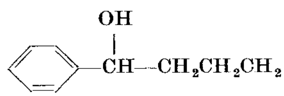
Compound	Structure II L	Structure II R	Lab.[a]	Salt	Serial number[c]	Species[b]	ED50 s.c. μM/kg with confidence limits	Molar P.R. (pethidine = 1·0)
1	CH_3	$COOCH_3$	JA	HCl	R 1137	M	319 (226–444)	0·25
2	CH_3	$COOC_2H_5$	JA	HCl	Pethidine	M	81 (78–85)	1·0
			ED			M	35 (29–42)	1·0
			JA			R	143 (130–160)	1·0
			EL			R	—	1·0
3	CH_3	O·COCH$_3$	JA	HCl	R 1160	M	81 (56–115)	1·0
			JA			R	59 (44–78)	2·4
4	CH_3	O.COC$_2$H$_5$	JA	HCl	R 1143	M	11 (8·5–13)	7·4
			JA			R	5·6 (4·9–6·3)	26
5	—CH_2	$COOC_2H_5$	JA	HCl	R 1324	M	> 278	< 0·3
			ED	base	N 7348	M	238 (211–270)	0·15
			JA	HCl	R 1324	R	> 278	< 0·5
			EL	—	—	R	—	0·32
6	—CH_2	O.COCH$_3$	ED	HCl	N 7706	M	36 (30–43)	1·0
			EL		W 14036	R	—	1·1
7		O.COC$_2$H$_5$	JA	HCl	R 1392	M	53 (39–72)	1·5
			ED		N 7683	M	9·1 (7·9–11)	3·8
			EL		W 10314	R	—	1·4
8	—CH_2CH_2	$COOCH_3$	JA	HCl	R 1246	M	128 (106–153)	0·62
9	—CH_2CH_2	$COOC_2H_5$	JA	HCl	R 1205	M	35 (29–37)	2·3
			ED		N 7288	M	13 (12–14)	2·7
			EL		—	R	—	2·6

10	 $—CH_2CH_2$	O.$COCH_3$	JA	HCl	R 1147	M	6·9 (6·1–8·1)	12
			ED	NH_2SO_3H	N 7714	M	0·53 (0·44–0·63)	66
			JA	HCl	R 1147	R	2·4 (2·0–2·8)	60
			EL	NH_2SO_3H	W 14265/2	R	—	72
11	 $—CH_2CH_2$	O.COC_2H_5	JA	HCl	R 1148	M	3·2 (2·7–4·0)	25
			ED	NH_2SO_3H	N 7740	M	0·53 (0·46–0·60)	66
			JA	HCl	R 1148	R	1·3 (1·0–1·7)	110
			EL	NH_2SO_3H	W 16492	R	—	69
12	 $—CH_2CH_2CH_2$	$COOC_2H_5$	JA	HCl	R 1368	M	3·6 (2·6–4·9)	23
			ED		N 7684	M	1·3 (1·2–1·5)	27
			JA		R 1368	R	7·2 (6·4–8·2)	20
			EL		W 13015	R	—	18
13	 $—CH_2CH_2CH_2$	O.$COCH_3$	JA	HCl	R 1400	M	1·3 (0·99–1·6)	62
			ED		N 7697	M	0·39 (0·35–0·45)	90
			JA		R 1400	R	0·54 (0·43–0·64)	265
			EL		W 13775	R	—	142
14	 $—CH_2CH_2CH_2$	O.COC_2H_5	JA	HCl.H_2O	R 1396	M	0·50 (0·44–0·57)	162
			ED	HCl	N 7744	M	0·11 (0·095–0·13)	318
			JA	HCl.H_2O	R 1396	R	0·25 (0·20–0·27)	572
			EL	HCl	W 16748	R	—	637
15	 $—CH_2CH_2CH_2CH_2$	$COOC_2H_5$	ED	HCl	N 7356	M	22 (21–24)	1·6
			EL		W 13181	R	—	2·8
16	 $—CH_2CH_2CH_2CH_2$	O.$COCH_3$	ED	HCl	N 7710	M	1·1 (0·95–1·3)	32
			EL		W 14113	R	—	39
17	 $—CH_2CH_2CH_2CH_2$	O.COC_2H_5	ED	HCl	N 7716	M	0·65 (0·57–0·75)	54
			EL		W 14306	R	—	108

[a] Laboratory: JA = Janssen *et al.*; ED = Eddy; EL = Elpern *et al.* [b] Species: M = mice; R = rats
[c] Serial number: R = Beerse serial number; N = NIH serial number; W = WIN (Sterling Winthrop serial number).

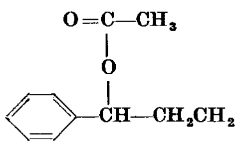
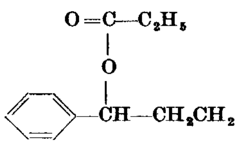
Table I. Analgesic activity of compounds related to pethidine—*cont.*

Compound	Structure II: L	Structure II: R	Lab.[a]	Salt	Serial number[c]	Species[b]	ED50 s.c. μM/kg with confidence limits	Molar P.R. (pethidine = 1·0)
18	—CH=CHCH$_2$	COOCH$_3$	JA	HCl	R 1255	M	15 (12–18)	5·4
19	—CH=CHCH$_2$	COOC$_2$H$_5$	JA	HCl	R 1000	M	2·5 (2·3–2·8)	32
			ED		N 7690	M	0·57 (0·49–0·67)	61
			JA		R 1000	R	3·6 (3·4–3·9)	40
			EL		W 13426	R	—	39
20	—CH=CHCH$_2$	O.COCH$_3$	JA	HCl	R 1312	M	0·99 (0·89–1·1)	82
			JA			R	0·38 (0·32–0·46)	376
			EL		—	R	—	189
21	—CH=CHCH$_2$	O.COC$_2$H$_5$	JA	HCl	R 1317	M	0·31 (0·29–0·36)	261
			ED	NH$_2$SO$_3$H	N 7718	M	0·054 (0·047–0·060)	650
			JA	HCl	R 1317	R	0·13 (0·11–0·15)	1100
			EL	NH$_2$SO$_3$H	W 14465/2	R	—	785
22	—CH=CHCH$_2$CH$_2$	COOCH$_3$	JA	HCl	R 1632	M	> 104	< 0·8
23		COOC$_2$H$_5$	JA	HCl	R 1581	M	173 (125–235)	0·47
24		O.COCH$_3$	JA	base	R 1593	M	8·3 (6·3–11)	9·8
25		O.COC$_2$H$_5$	JA	HCl	R 1588	M	6·0 (3·8–9·5)	14
26		COOC$_2$H$_5$	JA	base	R 992	M	> 285	< 0·3

27		$COOCH_3$	JA	HCl	R 993	M	2·4 (2·0–2·8)	34
						R	2·8 (2·4–3·1)	51
28		$COOC_2H_5$	JA	HCl	R 951	M	1·1 (1·0–1·2)	74
			ED		R 951	M	0·23 (0·21–0·27)	152
			JA		R 951	R	0·52 (0·47–0·60)	275
29		$COOCH_3$	JA	HCl	R 1338	M	6·3 (5·5–7·3)	13
30		$COOC_2H_5$	JA	HCl	R 1187	M	6·7 (5·5–8·2)	12
						R	7·5 (6·7–8·4)	19
31		$COOC_2H_5$	JA	base	R 971	M	31 (28–37)	2·6
			ED	HCl	oxphener-idine	M	8·5	4·1
32		$COOCH_3$	JA	base	R 2037	M	4·2 (3·4–5·1)	19
33		$COOC_2H_5$	JA	HCl	R 1406	M	0·82 (0·69–0·99)	99
			ED		N 7591	M	0·16 (0·15–0·18)	219
			JA		R 1406	R	0·50 (0·40–0·59)	286
34		$COOCH_3$	JA	base	R 1998	M	25 (15–41)	3·2
35		$COOC_2H_5$	JA	base	R 1475	M	8·1 (6·3–10)	10

[a] Laboratory: JA = Janssen *et al.*; Ed = Eddy; EL = Elpern *et al.* [b] Species: M = Mice; R = Rats
[c] Serial number: R = Beerse serial number; N = NIH serial number; W = WIN (Sterling Winthrop serial number).

Table I. Analgesic activity of compounds related to pethidine.—*cont.*

Compound	Structure II: L	Structure II: R	Lab[a]	Salt	Serial number[c]	Species[b]	ED50 s.c. μM/kg with confidence limits	Molar P.R. (pethidine = 1·0)
36		$COOC_2H_5$	JA	HCl	R 1408	M	1·5 (1·1–1·9)	54
						R	3·4 (2·9–4·0)	42
37		$O.COCH_3$	JA	HCl	R 1431	M	0·28 (0·20–0·37)	289
						R	0·23 (0·21–0·28)	622
38		$COOC_2H_5$	JA	HCl	R 1427	M	0·87 (0·74–1·0)	93
39		$O.COC_2H_5$	JA	base	R 1480	M	0·054 (0·042–0·068)	1500
			ED			M	0·011 (0·0094–0·012)	3180
			JA			R	0·047 (0·040–0·054)	3040

[a] Laboratory: JA = Janssen *et al.*; ED = Eddy; EL = Elpern *et al.* [b] Species: M = Mice; R = rats
[c] Serial number: R = Beerse serial number; N = NIH serial number; W = WIN (Sterling Winthrop serial number).

Experimental

Compounds 1–5, 7–14, 18–39 (Table I) were synthesised in Beerse,[9, 10] compounds 2, 5–7, 9–17, 19–21 at the Sterling Winthrop Research Institute[4, 5] and compounds 9 and 31 in Bethesda.[18] Details of the synthesis of the new compounds prepared in Beerse (22–25, 26, 32–39) will be published elsewhere.

All 39 compounds listed in Table I were tested for analgesic activity in mice, 15 of them both in Beerse and in Bethesda, 20 in Beerse only (JA) and 4 in Bethesda only (ED). Two previously described modifications to the 'hot plate method' were used.[8–10, 26–30]

Twenty-five of the 39 compounds of Table I were also tested for analgesic activity in rats, 10 of them both in Beerse and at the Sterling Winthrop Institute, 9 in Beerse only (JA) and the 6 others at the Sterling Winthrop Institute only (EL). In Beerse a previously described 'hot plate method'[29] was used. The Sterling Winthrop results, recently published by Elpern *et al.*,[4, 5] were obtained using a radiant heat method.

All compounds were injected subcutaneously. ED50 values and confidence limits ($P = 0 \cdot 05$) are expressed in micromoles per kilogram (μM/kg) body weight, and potency ratios (PR) are expressed on an equimolar basis (pethidine $= 1 \cdot 0$).

Results

A series of 8 compounds of structure II (Table I) were tested in the three laboratories using four different experimental methods. Ranking these potency ratios gives 4 rankings of 8 individuals (Ranking A) each or 8 rankings of 4 individuals (Ranking B) (Table II).

The coefficient of concordance W for the 4 rankings A ($n = 8$; $m = 4$) is $0 \cdot 94$ ($X_r^2 = 26 \cdot 3$; $\gamma = 7$; $P < 0 \cdot 01$). The concordance of the ranking of PR as obtained in 4 different experimental conditions is highly significant.

Inspection of rankings B shows however the PR's in mice (Beerse) to be almost systematically lower (roughly $2\frac{1}{2}$ times) than the three other sets of PR values, among which there is satisfactory agreement. The relatively high ED50 in mice (Beerse) of pethidine is responsible for this discrepancy.

Table II.

Compd. No.	PR				Ranking A				Ranking B			
	mice		rats		mice		rats		mice		rats	
	JA	ED	JA	EL	JA	ED	JA	EL	JA	ED	JA	EL
2	1	1	1	1	1	1	1	1	$2\frac{1}{2}$	$2\frac{1}{2}$	$2\frac{1}{2}$	$2\frac{1}{2}$
10	12	66	60	72	2	$4\frac{1}{2}$	4	5	1	3	2	4
11	25	66	110	69	4	$4\frac{1}{2}$	5	4	1	2	4	3
12	23	27	20	18	3	2	2	2	3	4	2	1
13	62	90	265	142	6	6	6	6	1	2	4	3
14	162	318	572	637	7	7	7	7	1	2	3	4
19	32	61	40	39	5	3	3	3	1	4	3	2
21	261	650	1100	785	8	8	8	8	1	2	4	3
									$11\frac{1}{2}$	$21\frac{1}{2}$	$24\frac{1}{2}$	$22\frac{1}{2}$

The following discussion will therefore be based on PR ratios recorded in Table I for pairs of compounds as determined using one technique only.

(1) *Analgesic activity increases about 20-fold when carbethoxy in II* ($R=COOC_2H_5$) *is replaced by propionoxy* ($R=OCOC_2H_5$) *regardless of the chemical structure of the substituent L.*

This general conclusion is based on the analysis of 19 pairs of PR values on 8 pairs of compounds II ($R=COOC_2H_5$ and $O.COC_2H_5$):

Species	Laboratory	PR ($O.CO.C_2H_5$) : PR ($COOC_2H_5$) average	min.	max.	No. of pairs
mice	Beerse	16·1	6·8	33·8	7
	Bethesda	18·0	10·7	25·3	4
rats	Beerse	27·4	26·0	28·6	3
	S. Winthrop	25·0	4·4	38·6	5
	Total	20·6	4·4	38·6	19

The data suggest a somewhat larger influence of $COOC_2H_5 \rightarrow O.COC_2H_5$ replacement on analgesic potency in rats than in mice.

(2) *The propionoxy esters (II; $R = O.COC_2H_5$) are about 3 times more active than the corresponding acetoxy esters (II; $R = OCOCH_3$).*

This general estimate is based on 18 available pairs of PR values for 7 compounds.

Species	Laboratory	PR ($O.CO.C_2H_5$) : PR ($OCOCH_3$) average	min.	max.	No. of pairs
mice	Beerse	3·3	1·4	7·4	5
	Bethesda	1·9	1·0	3·5	4
rats	Beerse	4·4	1·8	10·8	4
	S. Winthrop	2·7	0·96	4·5	5
	Total	3·1	0·96	10·8	18

The highest ratios (7·4 and 10·8) are found for the N–CH_3 derivatives, the lowest (0·96 and 1·0) for the N–phenethyl compounds.

(3) *The carbethoxy esters are about 4 times more active than the corresponding carbomethoxy esters.*

This estimate is based on 8 available pairs of PR values on 7 substances.

Species	Laboratory	PR ($COOC_2H_5$) : PR ($COOCH_3$) average	min.	max.	No. of pairs
mice	Beerse	3·6	1·1	5·9	7
rats	Beerse	5·4	—	—	1
		3·8			8

Changes in Substituted L in Compounds of Type II

(4) *A phenylpropyl derivative is about 6 times as active as the corresponding phenethyl derivative.*

The 11 available pairs of PR values for the 3 pairs of derivatives are as follows.

	Mice		Rats	
	Beerse	Bethesda	Beerse	S. Winthrop
$COOC_2H_5$	23/2·3=10·0	27/2·7=10·0	—	18/2·6=6·9
$O.COCH_3$	62/12 = 5·2	90/66 = 1·4	265/60 =4·4	142/72 =2·0
$O.CO.C_2H_5$	162/25 = 6·5	318/66 = 4·8	572/110=5·2	637/69 =9·2
average	7·2	5·4	4·8	6·0
	6·0 (min. 1·4; max. 10·0)			

(5) *A phenylpropyl derivative is about 7 times as active as the corresponding phenylbutyl derivatives.*

This estimate is based on the following pairs of PR values.

	Mice Bethesda	Rats S. Winthrop
$COOC_2H_5$	27/1·6=16·9	18/2·8=6·4
$O.COCH_3$	90/32 = 2·8	142/39 =3·6
$O.COC_2H_5$	318/54 = 5·9	637/108=5·9
average	8·5	5·3
	6·9 (min. 2·8; max. 16·9)	

Corresponding phenethyl- and phenylbutyl derivatives therefore are about equiactive (the average estimate for 6 pairs of PR values is 1·4; min. 0·64 and max. 2·1).

(6) *A phenylpropyl derivative is about 160 times as active as the corresponding* N-*benzyl derivative.*

This estimate is based on the following pairs of PR values listed in Table I.

	Mice		Rats
	Beerse	Bethesda	S. Winthrop
$COOC_2H_5$	—	27/0·15=180	18/0·32= 56
$O.CO.CH_3$	—	90/1·0 = 90	142/1·1 =129
$O.CO.C_2H_5$	162/1·5=108	318/3·8 = 84	637/1·4 =455

The total average ratio is 157 (min. 56; max. 455).

(7) $[C_6H_5CH{=}CHCH_2] \sim 11 \times [C_6H_5CH{=}CHCH_2CH_2]$

This estimate is based on only 4 pairs of PR values obtained in mice (Beerse).

$COOCH_3$	5·4/<0·84	= >6·4	
$COOC_2H_5$	32/0·47	= 6·8	average 11·3
$O.CO.CH_3$	82/9·8	= 8·4	
$O.CO.C_2H_5$	261/14	= 18·6	

(8) $[C_6H_5COCH_2CH_2] \sim 8 \times [C_6H_5COCH_2CH_2CH_2]$

Only 3 pairs of PR values are available to estimate this ratio, all three obtained in Beerse.

$COOCH_3$	mice	34/13	= 2·6	
$COOC_2H_5$	mice	74/12	= 6·2	average 7·8
$COOC_2H_5$	rats	275/19	=14·5	

(9) $[C_6H_5COCH_2CH_2] > 25 \times [C_6H_5COCH_2]$

The only pair of compounds available was tested only in mice (Beerse).

$COOC_2H_5$: 74/< 0·3 = > 24·7

(10) $[C_6H_5CHOHCH_2CH_2] \sim 8 \times [C_6H_5CHOHCH_2CH_2CH_2]$

An estimate based on the following PR values for mice (Beerse).

$COOCH_3$	19/3·2 = 5·9	average 7·9
$COOC_2H_5$	99/10 = 9·9	

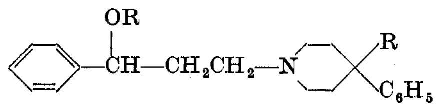
(11) $[C_6H_5CHOHCH_2CH_2] \sim 50 \times [C_6H_5CHOHCH_2]$

One pair of compounds (31/33) was tested in mice in Beerse and in Bethesda.

$COOC_2H_5$	Beerse	$99/2 \cdot 6 = 38$	average 46
$COOC_2H_5$	Bethesda	$219/4 \cdot 1 = 54$	

(12) $C_6H_5CHOR'CH_2CH_2$ ($R' = H$, $COCH_3$ or COC_2H_5):

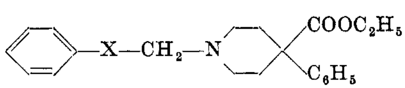
The influence of acylation and propionylation of the secondary alcohol function of aminopropanols of the type



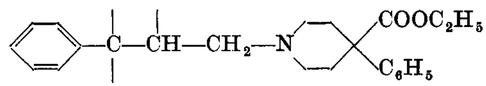
was not studied in detail. Acylation seems to decrease activity to a small extent, whereas the propionoxy compounds are about as potent as the alcohols from which they are derived. This is not surprising in view of the fact that hydrolysis of the propionoxy group to the secondary alcohol proceeds very rapidly in aqueous solution (unpublished data).

(13) The influence of chemical modifications in L on analgesic potency of carbethoxy esters ($COOC_2H_5$) of type II is summarized in Table III.

Table III.

Cmpd.	 X	PR (pethidine = 1·0) mice JA	mice ED	rats JA	rats ED	Ratios
1	$CHOHCH_2$	99	219	286	—	
2	$CHOCOC_2H_5CH_2$	93	—	—	—	1·3±0·2
3	$COCH_2$	74	152	275	—	
4	$CHOCOCH_3CH_2$	54	—	42	—	4·0±1·8
5	$CH{=}CH$	32	61	40	39	
6	CH_2CH_2	23	27	20	18	2·0±0·5
7	$COCH_2CH_2$	12	—	19	—	
8	CHOH	2·6	4·1	—	—	
9	CH_2	2·3	2·7	—	2·6	
10	$CH_2CH_2CH_2$	—	1·6	—	2·8	
11	$CH{=}CHCH_2$	0·47	—	—	—	
12	nil	<0·3	0·15	<0·5	0·32	

The most active derivatives, obviously, are of the type



the phenyl ring being connected with the nitrogen atom by a straight chain of 3 carbon atoms.

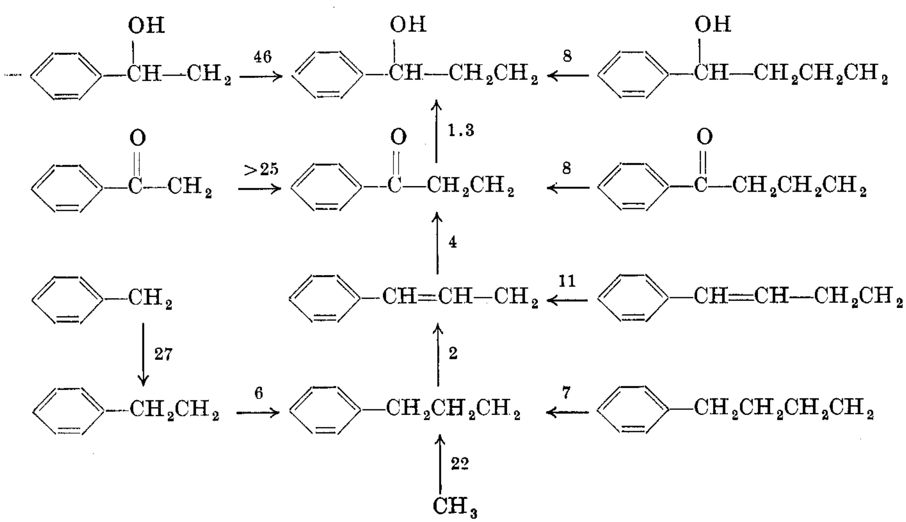
Conclusions

An attempt was made in the previous section to estimate in semi-quantitative terms the influence of systematic chemical modifications on analgesic potency in mice and in rats of pethidine derivatives of type II.

A combined summary of all these evaluations (PR for pethidine $= 1\cdot0$) is as follows:

(1) average PR ratios among the 4 types of esters studied are $O.COC_2H_5 \sim 3\ O.COCH_3 \sim 20\ COOC_2H_5 \sim 80\ COOCH_3$.

(2) the influence of substituent L on PR is roughly summarized below; the arrows pointing towards increased activity.*



* $A \xrightarrow{B} C$; $B = \mathrm{PR}(C) : \mathrm{PR}(A)$

Further experimental work and collaborative testing is obviously required to gain better insight into these structure-activity relationships. Until completely reproducible methods have been developed, all efforts to correlate structure with activity in quantitative terms are bound to yield only rough approximations.

Summary. An attempt is made to estimate in semi-quantitative terms the influence of systematic chemical modifications on analgesic potency in mice and in rats of a series of compounds related to pethidine.

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