RESEARCH PAPERS

A NEW SERIES OF POTENT ANALGESICS:

DEXTRO 2:2-DIPHENYL-3-METHYL-4-MORPHOLINO-BUTYRYLPYRROLIDINE AND RELATED AMIDES

PART I. CHEMICAL STRUCTURE AND PHARMACOLOGICAL ACTIVITY

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SUBSTITUTED diphenylpropylamines of general structure I, in which R is a radical and NAA' an open or closed tertiary amino group, have been shown by different workers to possess pronounced analgesic or atropine-like activity[1-8,14,16-22,24,25]. No known compound is both a

(I)
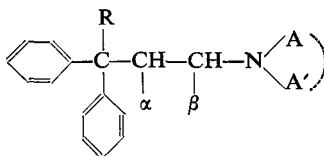
(I *a*, a = H, β = H; I *b*, a = CH_3, β = H; I *c*, a = H, β = CH_3)

potent analgesic and a potent atropine-like substance[1,5]. Which sort of activity predominates seems to depend, in the first place, upon the nature of substituent R of structure I[2].

Analgesics have been found among compounds of the methadone type, for example I, R = COC_2H_5, methadols and acylated methadols, I, R = $CHOR'·C_2H_5$; sulfones, I, R = $SO_2C_2H_5$; esters, I, R = $COOC_2H_5$; ketimines and acylated ketimines, I, R = C:$NR'·C_2H_5$[2,5, 16,17-24].

Atropine-like activity has been found among primary amides like R 79 (R = $CONH_2$), "reversed" amides like R 79, for example R = NH–COR', nitriles, R = CN, tertiary alcohols, R = OH, and unsubstituted amines R = H[1-8]. Within these groups of compounds the relative potency depends not only upon the nature of R, but also upon the configuration of the basic side chain, $CH\alpha·CH\beta·NAA'$.

Potent analgesics of type I are usually dimethylamino-, morpholino-, piperidino- or pyrrolidino-derivatives.

Open dialkylamines with alkyl groups other than methyl have generally little activity, the analgesic activity decreasing with increasing size of the alkyl groups.

Only a few heterocyclic amino analogues of the pyrrolidino-, piperidino-, and morpholino-derivatives are known; they were found to be less active than the parent compounds.

Quaternisation of tertiary amines of type I decreases the analgesic activity, but increases the atropine-like activity[6].

The presence of the methyl group on the basic side-chain (Ia → Ib or Ic) generally increases the analgesic activity and lessens the atropine-like activity. Ketones, R = COC_2H_5, primary amides, R = $CONH_2$, and nitriles, R = CN of type Ic are more active than their isomers of type Ib. Some acetylmethadols of type Ib however are more active than their isomers of type Ic.

Some racemates of type Ib and Ic have been resolved, and in all, the analgesic or atropine-like activity is found with only one of the optical isomers.

The spatial configuration of the analgesically active isomers of type Ic, NAA' = $N(CH_3)_2$, is identical and related to that of D-(-)-alanine[11-13].

A large number of modifications of structure I have been made by attacking the molecule at all points[2].

In general, reduction or complete loss of analgesic activity occurs when one or both phenyl groups are substituted or replaced by other groups, or when the side chain is lengthened, shortened, or branched with groups other than methyl.

A number of new chemical modifications of structure I have not yet been examined, and the available information on the pharmacological properties of many of the known derivatives is poor and often conflicting[2]. We therefore decided to continue our research program[1-8] and to investigate a series of secondary and tertiary amides of type I[8], R = CONR'(R' = secondary or tertiary amide group). The synthesis and physico-chemical properties of the new compounds, listed in Table IV, will be described elsewhere.

PHARMACOLOGICAL METHODS

Analgesic Activity in Mice

The analgesic activity in mice was measured with an adaptation of the "hot plate" method[17-21]. Male albino mice of 20–30 g. and of a mixed inbred strain were used.

The hot plate was a restraining cylinder on a copper bath containing equal parts of boiling (55°–55·5°) acetone and ethyl formate[18,21].

The reaction time is the interval, measured in intervals of 2×10^{-1} seconds, between the moment the mouse reaches the hot plate and the moment the animal either licks its feet or jumps out of the cylinder. All other signs of discomfort, such as kicking of the hind legs, dancing around the cylinder are disregarded.

Using groups of five mice, the reaction time is measured 10 and 5 minutes before and 10, 20, 30, 45, 60, 90, 120, 180 and 240 minutes after subcutaneous injection or oral administration of 0·1 ml./10 g. body weight of an aqueous solution. The "normal reaction time" is defined as the average of both reaction times, estimated 10 and 5 minutes before giving the drug. The response was considered to be positive when the reaction time after injection was longer than 30 seconds at least once, or when three

or more readings exceeded the normal reaction time by a factor of three or more. All responses were negative in 300 mice, injected with saline or water over a period of one year.

The results were statistically evaluated using the graphical method of Litchfield and Wilcoxon[9], and expressed using the following symbols: ED50: median effective dose (mg./kg,); L.L. and U.L.: lower and upper fiducial (confidence) limits; S = slope; P.R. = potency ratio; f_{ED50}, f_s and $f_{P.R.}$ = factors for computing confidence limits (P = 0·05) of ED50, S and P.R.; s.c. = subcutaneous injection; and or = oral administration.

The distribution of the differences between the first and second estimation of the "normal reaction time" on 1000 untreated mice is shown in Table I.

TABLE I

DISTRIBUTION OF DIFFERENCES BETWEEN THE FIRST AND SECOND ESTIMATION OF
NORMAL REACTION TIME ON 1000 MICE

Seconds	Frequency		Total	Eddy[18,21]
	Positive	Negative		
			per cent	per cent
0		108	10·8	19·6
0·2–1·0	298	384	68·2	42·6
1·2–2·0	72	99	17·1	27·7
2·2–3·0	12	20	3·2	8·1
3·2–4·0	3	4	0·7	2·0
Total	385	507		

Statistical analysis of the frequency distributions of the normal reaction time, with 20 successive groups of 1000 mice during about one year, showed insignificant differences between these populations. The average normal reaction time for a group of 10,000 successively examined mice was 4·96 seconds, compared with the significantly different 9·51 seconds figure, reported by Eddy (Fig. 1). Ninety per cent of our values fall within the range of 3·3 to 7·0 seconds (Eddy: 6 to 13 seconds). There was no significant correlation of body weight and normal reaction time. The difference between the lowest and the highest of five ED50 values for morphine hydrochloride, estimated during a period of one year, was also statistically insignificant (subcutaneous injection). Rank correlation analysis failed to show a significant correlation of body weight (15 to 35 g.) and frequence of positive analgesic response after subcutaneous injection of 10 mg./kg. morphine hydrochloride.

For 150 substances with an ED50 value of 100 mg./kg. (subcutaneous injection) or less, the average slope value S was 1·58. The highest value of S was 2·74 and the lowest was 1·10; 90 per cent of these 150 values fall within the range of 1·20 to 2·20. The average f_s-value for this whole group was 1·255. In some instances therefore the dose-effect curves of two substances deviated significantly from parallelism (S.R. exceeds $f_{s.R.}$). A few examples are given in Table II.

Mydriatic Activity in Mice

The mydriatic activity in mice after subcutaneous or oral administration was estimated as described previously[1-3,5,7]. The same animals were used

for the simultaneous measurement of the analgesic and mydriatic effects.

The mydriatic effect was considered positive when the pupil diameter equalled or exceeded 30/25 mm. at 10, 20, 30, 60, 90, 120, 180, 240, 300, 360 or 420 minutes after giving a drug. In a series of 300 mice, injected with water or saline, all mydriatic responses were negative. The results were statistically evaluated and expressed as before.

TABLE II

ANALGESIC ACTIVITY IN MICE AND RATS BY SUBCUTANEOUS INJECTION
POTENCY RATIO, P.R.: MORPHINE HYDROCHLORIDE = 1·00

		P.R.†	L.L.†	U.L.†	$f_{P.R.}$†	S.R.†	$f_{S.R.}$†
R875	M	18·5	16·7	20·5	1·11	1·06	1·40
	R	40·5	33·0	49·9	1·23	1·31	1·20*
R610	M	9·60	8·65	10·7	1·11	1·06	1·10
	R	23·4	17·1	32·1	1·37	1·01	1·47
R660	M	8·70	7·91	9·57	1·10	1·01	1·23
	R	30·6	21·3	44·1	1·44	1·14	1·45
R888	M	1·54	1·38	1·72	1·12	1·01	1·27
	R	1·20	0·97	1·49	1·24	1·14	1·22
R530	M	0·88	0·80	0·96	1·10	1·03	1·10
	R	0·48	0·34	0·68	1·41	1·18	1·45
Heroin	M	6·00	5·46	6·66	1·11	1·11	1·16
	R	15·0	11·7	19·2	1·28	1·22	1·20*
Phenadoxone HBr ..	M	4·90	4·29	5·59	1·14	1·06	1·34
	R	6·52	5·05	8·41	1·29	1·07	1·20
Methadone HCl ..	M	2·32	2·11	2·55	1·10	1·10	1·20
	R	3·06	2·28	4·10	1·34	1·05	1·44
N-morpholino-ethyl-nor- pethidine 2 HCl	M	0·65	0·52	0·81	1·25	1·27	1·47
	R	0·65	0·47	0·90	1·38	1·03	1·35
Pethidine HCl	M	0·43	0·39	0·47	1·10	1·19	1·13*
	R	0·28	0·21	0·37	1·31	1·01	1·26
Codeine phosphate ..	M	0·23	0·21	0·26	1·11	1·11	1·23
	R	0·11	0·08	0·14	1·30	1·01	1·25

* The curves deviate significantly, 19/20 probability from parallelism (S.R. exceeds $f_{S.R.}$).
† For definition see page 383.

Analgesic Activity in Rats

The analgesic activity in rats was estimated by the hot plate method described for mice, except that the bath was bigger.

Male albino rats of an inbred Wistar-strain, weighing from 100 to 250 g., were used.

The copper bath (diameter: 40 cm., height: 15 cm.) contains 4 litres of a boiling mixture of equal parts of acetone and ethyl formate (55° to 55·5°). A restraining glass cylinder had the following dimensions; height 25 cm., internal diameter 26·5 cm., and external diameter 27·5 cm.

About 95 per cent of all animals eventually lick their feet after being dropped on to the hot plate and about one rat in 20 learns to jump out of the cylinder.

The frequency distribution of 1500 successively determined "normal reaction times" is shown in Figure 1. The adopted experimental design was practically identical with the one described for mice. The same

definitions of "reaction time", "normal reaction time" and "positive response" were adopted. Groups of ten rats were used and subcutaneously injected with 0·2 ml./100 g. weight of an aqueous solution containing various amounts of the drugs. The pupil diameter was not measured. The results were statistically evaluated and expressed as before. No significant rank correlation could be detected with body weight and normal reaction time, although heavy rats jump out of the cylinder oftener than light ones.
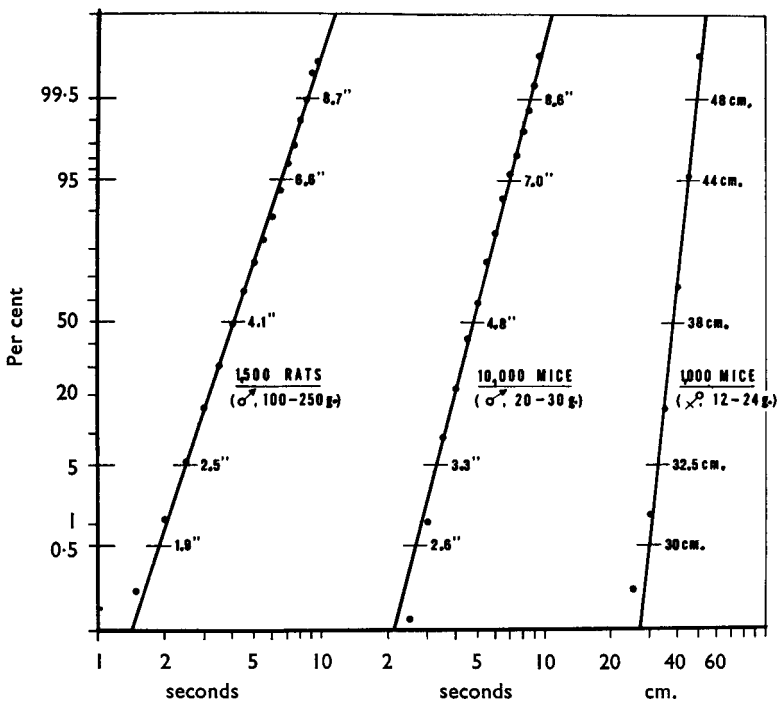

FIG. 1. Frequency distribution of the "normal reaction time" in seconds on 1500 rats and 10,000 mice, and of the distance from pylorus to appendix in cm. of 1000 mice.

Relative Atropine-like Activity In Vitro

The atropine-like activity was evaluated as previously described[1–4,6,7], using the inhibition of acetylcholine-induced spasms on the isolated intestine of rabbits as the criterium of activity, and atropine sulphate as the standard. All potency ratios (P.R.), calculated on an equimolar basis, are based on the results obtained with 3 × 12 doses of atropine and 3 × 12 doses of the substance investigated.

Inhibition of the Gastrointestinal Propulsion of a Charcoal Suspension in Mice

Groups of ten young female albino mice, 12 to 24 g., 2 to 4 months old of a mixed inbred strain, fasted overnight, were injected intraperitoneally

with 0·1 ml./10 g. weight of an aqueous solution containing varying amounts of the drug. One hour later the animals were given by stomach tube 0·3 ml. of an aqueous suspension containing 10 per cent charcoal and 5 per cent gum acacia. Two hours after the charcoal meal, the mice were killed, the intestines immediately excised from cardia to anus, and carefully laid out on clean white glass or stainless steel for inspection and measurement of the distances "pylorus to anus" and "pylorus to appendix". In 300 control mice, which were injected with saline only and given charcoal by stomach tube in the course of one year, the appendices of all were filled with charcoal (black appendix). Pretreatment with increasing doses of substances like analgesics or antispasmodics, which are known to depress gastrointestinal motility, increased the proportion of "white appendices" (no charcoal detected inside the appendix) in these experimental conditions. An all-or-none criterium was therefore adopted, the effect being considered "positive" when the appendix was "white", and "negative" when the appendix was "black" (contained some charcoal).

TABLE III

RELATION OF BODY WEIGHT AND DISTANCE FROM PYLORUS TO APPENDIX

Distance from pylorus to appendix cm.	Weight in g.			
	10–15	15·5–20	20·5–25	Total
20·5–25	0	0	1	1
25·5–30	5	6	1	12
30·5–35	56	78	11	145
35·5–40	116	309	78	503
40·5–45	21	172	101	294
45·5–50	1	24	19	44
50·5–55	0	0	1	1
Total	199	589	212	1000

In our experience the frequently used quantitative criterium, the distance traversed by the charcoal meal, expressed as the proportion of the total length of the intestine is unsatisfactory, because of the inaccuracy with which these measurements can be made and of the very flat dose-effect curves thus obtained. The results were statistically evaluated using the graphical method of Litchfield and Wilcoxon[9]. Observations on 1000 female albino mice, weighing from 10 to 25 g. and 2 to 4 months of age, showed that the distance from pylorus to appendix slowly increases with increasing weight. (Table III.)

As shown in Figure 1, 99 per cent of these values fall between 30 and 48 cm. (average: 38·6 cm.). In spite of these variable intestinal lengths, we were unable to detect a significant rank correlation of body weight or intestinal length and percentage positive effects in large groups of mice treated with ED40 to ED60 doses of R 875, R 79 (Priamide), morphine hydrochloride, atropine sulphate and chlorpromazine hydrochloride.

RESULTS

Analgesic Activity in Mice and Chemical Structure

The analgesic activity in mice by subcutaneous injection of 21 secondary and 58 tertiary amides of type I are listed in Table IV. Some 38 primary

amides, ketones of the methadone type, esters, alcohols, ketimines and acetylketimines of structure I, as well as 12 miscellaneous analgesics are included in Table IV for comparison. The relation between analgesic activity in mice and chemical structure of secondary and tertiary amides of structure I, can be described in the following way.
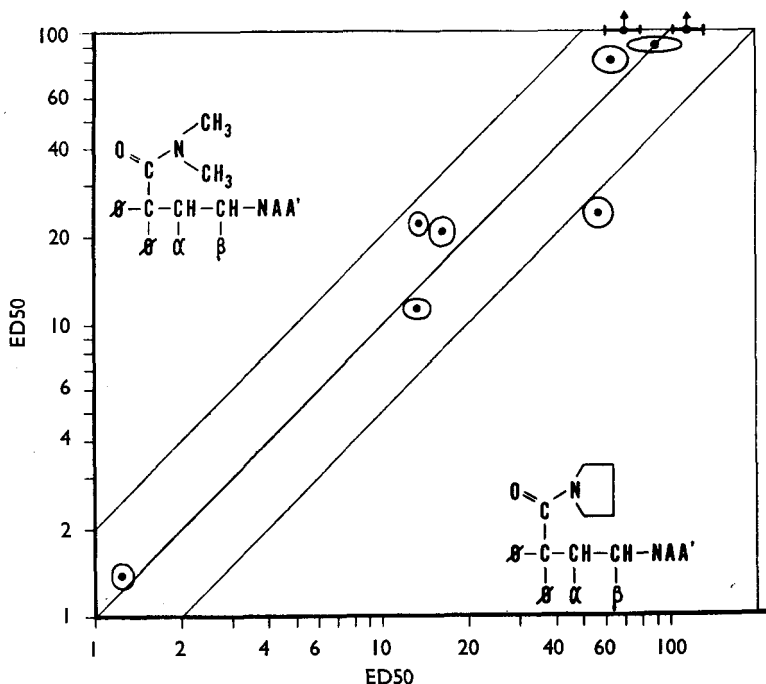

FIG. 2. The analgesic activity in mice by subcutaneous injection of 9 basic butyryl-pyrrolidines and of 9 corresponding butyryl-dimethylamines. The confidence limits, P 0·05 are shown graphically.

The Amide Group (R = CONHR' or CONR'R")

Highest analgesic activity was found among *N*-pyrrolidine- and *NN*'-di-methylamides. As shown in Figure 2, the corresponding derivatives of these two amides show about the same activity. Considerable loss of activity occurs when the tertiary amide group is derived from an open amine having alkyl-substituents other than methyl or from a cyclic amine larger than pyrrolidine. The most active secondary amides are *N*-ethyl-derivates, a few of them being about as active as pethidine.

α and β

A methyl group in the α-position of the side chain (type I*b*), increases the analgesic activity; inactive unbranched substances (I*a*) may even become as active as morphine when branched with a methyl-group in the α-position. This advantageous effect is more pronounced among tertiary- than among secondary amides. A methyl group in the β-position of the

side chain gives less active compounds than their α-methyl isomers of type I*b*, and as a rule even less active than their unbranched analogues. Most of them are completely inactive. Lengthening, shortening or branching the chain joining the tertiary nitrogen atom and the quaternary carbon atom with groups other than methyl causes reduction of activity.
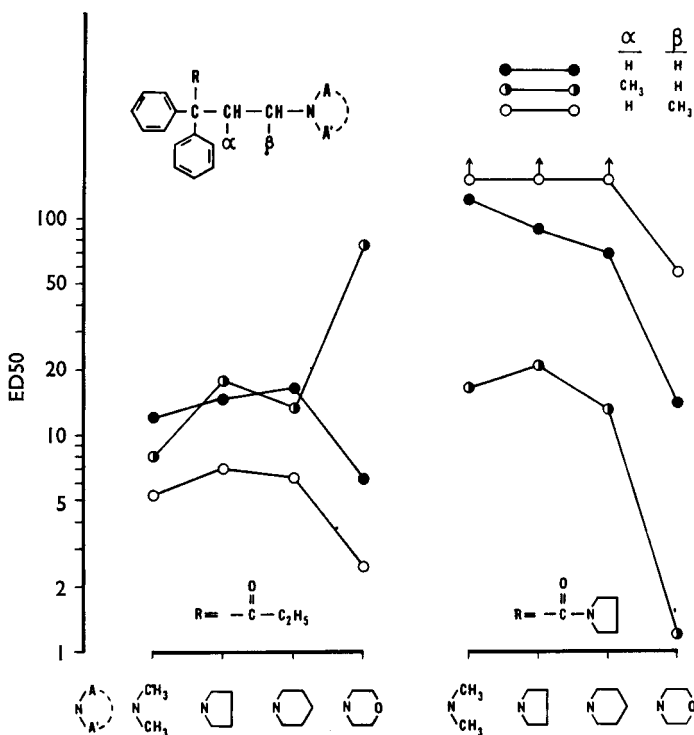

FIG. 3. The analgesic activity in mice by subcutaneous injection of 12 basic ketones of the methadone-type (R = COC_2H_5) and of the 12 corresponding basic pyrrolidino-amides of the R 610-type. The substances with a methyl-group in α- or β-position are the racemic mixtures; one of the two optical isomers is about twice as active as the racemate; the other optical isomer is inactive.

The various effects of methyl-branching in the α- and β-position on the analgesic activity of representative members of the 2:2-diphenyl-4-amino-butyryl-pyrrolidino-, and of the 4:4-diphenyl-6-amino-hexan-3-one-, (methadone) type are graphically represented in Figure 3.

These effects are more pronounced among basic amides than among ketones of type I.

Whereas isomethadone-like aminoketones may be more or less active than the unbranched parent compounds, the introduction of a methyl group in β-position increases the analgesic activity by about two and a half times. The fact that the β-methyl substituted amides are nearly inactive might therefore be more surprising than the high activity of the α-methyl analogues.

The Basic Group NAA'

The most active analgesics in mice and rats are basic amides with a morpholino group in the NAA' position. Among tertiary amides with a methyl-group in the α-position, the dimethylamine-, pyrrolidine- and piperdine analogues were also found to cause analgesia. They are about as active as morphine, but their β-methyl-isomers as well as the unbranched
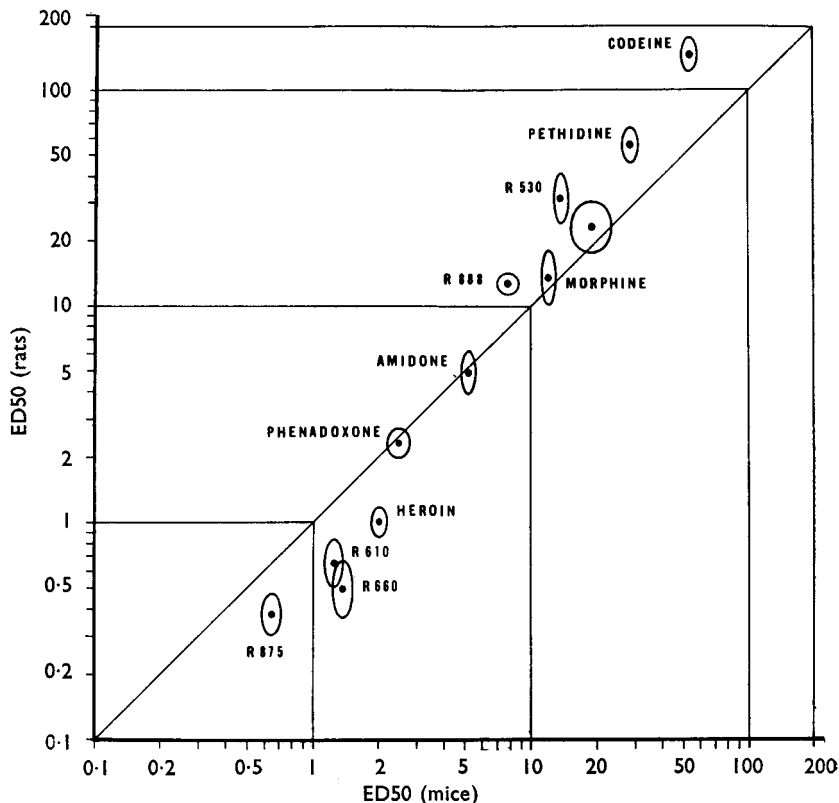

FIG. 4. Analgesic activity in mice versus analgesic activity in rats of 12 compounds listed in Table IV by subcutaneous injection. The confidence limits (P 0·05) of the ED50 values are shown graphically.

parent compounds are nearly inactive. All known analgesically active dimethylamino-derivatives of type I (NAA' $= N(CH_3)_2$) are proportionally inactivated by replacement of one or both methyl groups by alkyl groups of increasing size. Ring-substitution with alkyl groups in derivatives of heterocyclic amines also results in reduction of activity.

All known quaternary amines of type I are much less active than the tertiary amines from which they are derived.

Optical Isomers

The presence of the methyl-group in the α- or β-position introduces an asymmetric carbon atom. In the α-methyl series, one of the optical

isomers of each enantiomorphic pair is about twice as active as the racemic mixture, while the other optical isomer is devoid of significant analgesic activity. The spatial configurations of active optical isomers of type I will be discussed elsewhere.
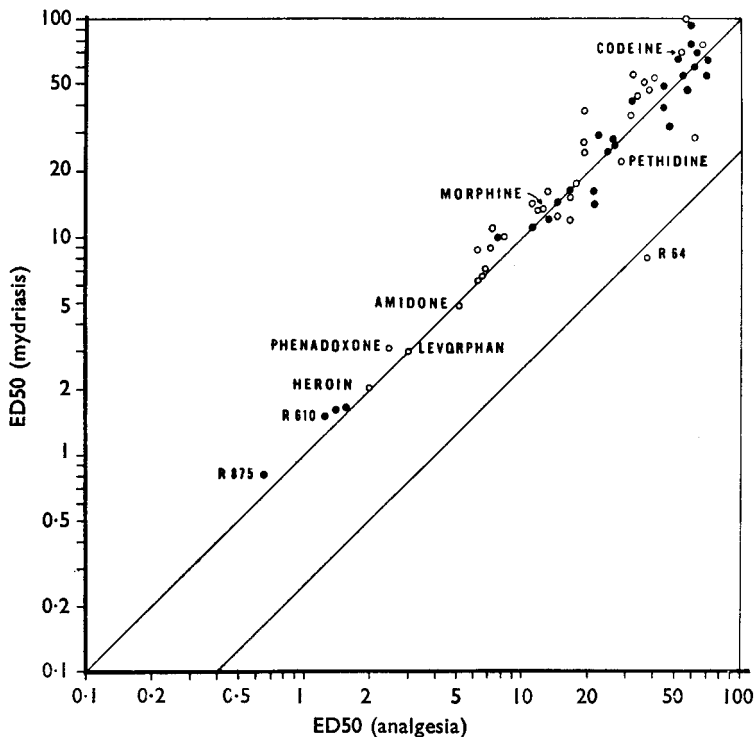

FIG. 5. Mydriatic versus analgesic activity in mice by subcutaneous injection of 29 basic amides related to R 875 (black circles) and of 33 other analgesically active substances (white circles), listed in Table IV.

Modification of the Diphenylmethane-group

The unpublished data from tests which we have made with this group show that replacement of one or both phenyl groups by hydrogen, various alkyl groups or other aryl-groups as well as substitution by an alkyl group, an alkoxy group or a halogen atom, invariably leads to less active compounds.

Analgesic Activity in Rats

As shown in Figure 4, significant correlation is observed with the analgesic activities in mice and rats by subcutaneous injection. Six compounds with an ED50 in mice of less than 10, also show an ED50 rat: mouse ratio of less than one; the other six compounds, shown in Figure 4, having ED50 in mice values of 10 or more, also have ED50 rat: mouse ratios greater than one. In four instances, however, this ratio was not significantly different from one.

Atropine-like Activity In Vitro and *Mydriatic Activity in Mice*

The compounds listed in Table IV have been tested for relative atropine-like activity *in vitro*. All secondary and tertiary amides, ketones, esters, methadols, acetylmethadols, ketimines, and acetylketimines of type I are devoid of significant activity (P.R. < 0·02 atropine). As shown in Figure 5, a significant correlation is found in mice with the analgesic and the mydriatic action of the analgesically active compounds listed in Table IV.
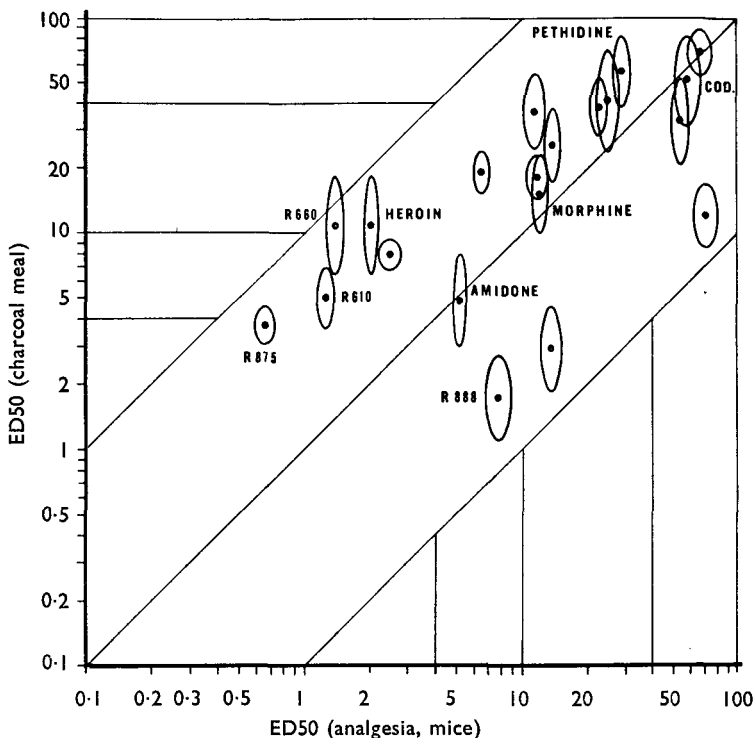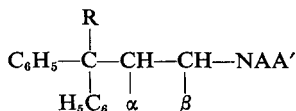

FIG. 6. The relation between the analgesic activity by subcutaneous injection in mice and the activity in the charcoal test in mice of twenty analgesically active compounds listed in Table IV. The confidence limits (P 0·05) of the ED50-values are graphically represented.
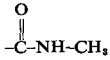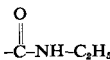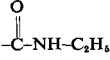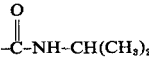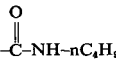
This typical relationship has been discussed previously[5]. A number of analgesically inactive secondary and tertiary amides of type I however are quite active mydriatics in mice. Since these substances are devoid of atropine-like action *in vitro* and the mydriatic activity after subcutaneous injection develops slowly—the maximal effect being seen after 2 to 3 hours, it seems likely that metabolic transformation into active metabolites occurs, possibly into the corresponding primary amides.

Inhibition of the Gastrointestinal Propulsion of a Charcoal Meal in Mice

All known analgesics significantly inhibit the gastrointestinal propulsion of a charcoal meal in mice, but we find no obvious quantitative correlation

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TABLE IV

$$\underset{\underset{H_5C_6 \quad \alpha \quad \beta}{}}{C_6H_5-\overset{\overset{R}{|}}{C}-CH-CH-NAA'}$$

Serial number	R	α	β	NAA'	Salt	Animals*	ED50	L.L.†	U.L.†	S†	f_s
R802	$-\overset{O}{\overset{\|}{C}}$-NH-CH₃	CH₃	H	N(CH₃)₂	HCl	A M	146 >150	108 —	197 —	1·81 —	1·45 —
R637	,,	H	H	N (ring)	base	A M	>100 >10	— —	— —	— —	— —
R608	,,	H	H	N (ring)	,,	A M	>100 3·19	— 2·64	— 3·86	— 1·61	— 1·10
R588	,,	H	H	N O (ring)	,,	A M	43·8 39·0	35·0 32·0	54·8 47·6	1·75 1·63	1·60 1·44
R766	,,	CH₃	H	,,	HCl	A M	44·1 48·6	40·1 43·4	48·5 54·4	1·18 1·23	1·06 1·09
R727	,,	H	CH₃	,,	base	A M	53·9 53·9	48·1 48·6	60·4 59·8	1·31 1·28	1·07 1·06
R750	$-\overset{O}{\overset{\|}{C}}$-NH-C₂H₅	H	H	N(CH₃)₂	,,	A M	>100 >25	— —	— —	— —	— —
R847	,,	CH₃	H	,,	C₂H₂O₄	A M	145 98·0	116 74·2	181 129	1·55 1·47	1·16 1·17
R646	,,	H	H	N (ring)	base	A M	>100 >50	— —	— —	— —	— —
R605	,,	H	H	N (ring)	,,	A M CH	>50 1·60 1·50	— 1·38 0·88	— 1·86 2·55	— 1·64 10·2	— 1·12 2·20
R1123	,,	CH₃	H	,,	,,	A M CH	54·0 27·2 33·9	45·4 23·5 27·6	64·3 31·6 41·7	1·58 1·48 1·49	1·27 1·19 1·37
R590	,,	H	H	N O (ring)	,,	A M	47·0 32·0	42·3 28·6	52·2 35·8	1·28 1·20	1·11 1·07
R685	,,	CH₃	H	,,	,,	A M	25·9 26·0	23·9 22·4	28·1 30·2	1·43 1·91	1·20 1·85
R680	$-\overset{O}{\overset{\|}{C}}$-NH-C₂H₅	H	CH₃	N O (ring)	base	A M	62·0 65·5	53·0 59·0	72·5 72·7	1·50 1·31	1·22 1·09
R979	,,	H	H	N(iC₃H₇)₂	,,	A M	>50 25·0	— 22·5	— 27·8	— 1·26	— 1·06
R600	$-\overset{O}{\overset{\|}{C}}$-NH-CH(CH₃)₂	H	H	N (ring)	,,	A M	>100 1·99	— 1·46	— 2·71	— 1·54	— 1·22
R580	,,	H	H	N O (ring)	,,	A M	65·5 16·0	59·5 12·1	72·1 21·1	1·17 1·80	1·07 1·24
R760	,,	CH₃	H	,,	,,	A M	82·0 73·8	72·6 65·3	92·7 83·4	1·19 1·30	1·10 1·15
R591	$-\overset{O}{\overset{\|}{C}}$-NH-nC₄H₉	H	H	,,	,,	A M	>100 >100	— —	— —	— —	— —

* Analgesic activity:
    A: in mice (S.C.)
    AO: in mice (oral)
    AR: in rats (S.C.)

Mydriatic activity:
    M: in mice (S.C.)
    MO: in mice (oral)

Charcoal meal:
    CH: in mice (I.P.)

† For definition see page 383

TABLE IV—continued

Serial number	R	α	β	NAA'	Salt	Animals*	ED50	L.L.	U.L.	S	f_s
R765	"	CH₃	H	"	"	A	>100	—	—	—	—
						M	>100	—	—	—	—
R909	−C(O)−NH−C(CH₃)₃	CH₃	H	"	"	A	>100	—	—	—	—
						M	>100	—	—	—	—
R910	−C(O)−NH−CH₂−C₆H₅	CH₃	H	"	"	A	>100	—	—	—	—
						M	>100	—	—	—	—
R731	−C(O)−N(CH₃)₂	H	H	N(CH₃)₂	"	A	>100	—	—	—	—
						M	>50	—	—	—	—
R777	"	CH₃	H	"	"	A	21·0	18·6	23·7	1·71	1·42
						M	14·3	12·7	16·2	1·51	1·30
R711	"	H	H	(pyrrolidine)	"	A	91·0	85·0	97·4	1·12	1·06
						M	8·25	6·76	10·1	1·44	1·09
R566 (ref. 15)	"	H	H	(piperidine)	"	A	>100	—	—	—	—
						M	9·4	7·58	11·7	1·35	1·10
R700	"	CH₃	H	"	"	A	11·4	10·4	12·5	1·59	1·12
						M	11·0	10·2	11·9	1·49	1·09
R555	"	H	H	(morpholine)	"	A	22·3	20·5	24·3	1·72	1·11
						M	29·1	26·9	31·4	1·56	1·07
						AO	44·6	39·1	50·8	1·34	1·17
						MO	63·0	50·4	78·8	1·79	1·74
						CH	38·3	28·0	52·5	1·67	1·35
R660	"	CH₃	H	"	"	A	1·38	1·25	1·52	1·71	1·22
						M	1·59	1·45	1·74	1·53	1·16
						AO	7·90	6·58	9·48	1·78	1·35
						MO	9·75	8·71	10·9	1·36	1·09
						AR	0·49	0·36	0·67	1·67	1·41
						CH	10·9	6·42	18·3	2·77	2·12
R630	"	CH₃	H	"	HCl	A	1·54	1·38	1·72	1·48	1·09
						M	1·65	1·42	1·91	1·77	1·18
						AO	15·0	12·8	17·6	1·87	1·33
						MO	19·0	17·8	20·3	1·28	1·06
R676	−C(O)−N(CH₃)	H	CH₃	(morpholine)	base	A	24·5	21·7	27·7	1·60	1·13
						M	24·2	22·8	25·7	1·16	1·04
						CH	40·2	23·4	69·1	2·43	2·40
R876	"	H	H	(2,6-dimethylmorpholine)	HCl	A	79·9	71·3	89·5	1·45	1·18
						M	77·0	68·1	87·0	1·55	1·23
R881	−C(O)−N(CH₃)−C₂H₅	H	H	N(CH₃)₂	base	A	>100	—	—	—	—
						M	>25	—	—	—	—
R883	"	H	H	(pyrrolidine)	"	A	>100	—	—	—	—
						M	3·30	2·70	4·03	1·43	1·17
R869	"	H	H	(piperidine)	"	A	>100	—	—	—	—
						M	4·01	3·29	4·89	1·44	1·17
R868	"	H	H	(morpholine)	HCl	A	70·0	57·9	84·7	1·30	1·19
						M	53·8	45·3	63·1	1·26	1·16
R850	"	CH₃	H	"	base	A	26·0	23·2	29·1	1·50	1·34
						M	27·5	25·0	30·3	1·35	1·22
R732	−C(O)−N(C₂H₅)₂	H	H	N(CH₃)₂	base	A	>50	—	—	—	—
						M	>50	—	—	—	—
R567	"	H	H	(piperidine)	"	A	>75	—	—	—	—
						M	6·35	5·08	7·94	1·57	1·24

TABLE IV—continued

Serial number	R	α	β	NAA'	Salt	Animals*	ED50	L.L.	U.L.	S	f_s
R945	,,	CH_3	H	,,	,,	A M	>50 19·0	— 16·7	— 21·7	— 1·35	— 1·10
R974	,,	H	CH*	,,	,,	A M	>25 4·08	— 3·11	— 5·34	— 1·46	— 1·22
R558	,,	H	H	N—O (morpholine)	,,	A M	62·0 60·0	57·1 55·1	67·3 65·4	1·18 1·24	1·08 1·06
R775	,,	CH_3	H	,,	,,	A M	32·1 42·2	29·2 37·7	35·2 47·3	1·34 1·35	1·05 1·06
R545	–C(=O)–N (pyrrolidine)	H	H	$N(CH_3)_2$	,,	A M	118·0 77·0	95·2 65·3	146 90·7	1·59 1·37	1·32 1·15
R554	,,	CH_3	H	,,	,,	A M	16·3 16·5	14·8 14·6	17·9 18·7	2·16 2·35	1·33 1·42
R616	,,	H	CH_3	,,	HCl	A M	>100 >20	— —	— —	— —	— —
R561	,,	H	H	$N(C_2H_5)_2$	,,	A M	>100 91·0	— 69·5	— 19·2	— 1·55	— 1·55
R535	,,	H	H	N (pyrrolidine)	base	A M	89·5 >20	71·2 —	111·3 —	1·58 —	1·57 —
R695	,,	CH_3	H	,,	,,	A M	20·9 16·0	18·8 13·8	23·2 18·6	1·41 1·60	1·11 1·22
R720	–C(=O)–N (pyrrolidine)	H	CH_3	N (pyrrolidine)	base	A M	>50 >50	— —	— —	— —	— —
R540	,,	H	H	N (piperidine)	,,	A M CH	70·0 15·0 12·0	61·4 12·6 8·51	79·8 17·9 16·9	1·30 1·40 1·99	1·10 1·28 1·40
R675	,,	CH_3	H	,,	,,	A M AO MO AR CH	13·2 12·3 33·5 43·9 >25 2·90	11·9 11·1 25·6 36·6 — 1·84	14·7 13·5 43·9 52·7 — 4·58	2·14 1·52 1·90 1·90 — 3·25	1·28 1·11 1·84 1·30 — 1·65
R888	,,	CH_3	H	,,	dextro-base	A M AO MO AR CH	7·80 10·1 15·7 19·7 12·5 1·71	6·96 8·56 13·4 17·6 11·2 1·08	8·74 11·9 18·4 22·1 14·0 2·70	1·70 2·15 2·06 1·60 1·68 3·25	1·26 1·60 1·46 1·19 1·16 1·65
R982	,,	H	CH_3	,,	HCl	A M CH	>50 13·0 33·0	— 10·7 19·6	— 15·9 55·4	— 1·17 1·96	— 1·15 1·89
R530	,,	H	H	N—O (morpholine)	base	A M AO MO AR CH	13·6 14·6 63·0 60·8 31·5 25·3	12·7 14·0 55·3 55·8 23·7 16·9	14·6 15·2 71·8 66·3 41·9 38·0	1·64 1·29 1·30 1·18 1·74 2·25	1·09 1·03 1·22 1·08 1·41 1·88
R610	,,	CH_3	H	,,	,,	A M AO MO AR CH	1·25 1·50 4·75 7·00 0·64 5·00	1·13 1·38 4·32 6·19 0·50 3·60	1·39 1·64 5·23 7·91 0·82 6·95	1·79 1·58 1·58 1·49 1·49 2·11	1·09 1·05 1·20 1·24 1·44 1·31
R875	,,	CH_3	H	,,	dextro-base	A M AO MO AR CH	0·645 0·725 3·20 5·20 0·37 3·72	0·58 0·64 2·83 4·33 0·33 3·05	0·72 0·82 3·62 6·24 0·40 4·54	1·64 1·78 1·89 2·28 1·21 1·68	1·07 1·10 1·23 1·46 1·06 1·17
R898	,,	CH_3	H	,,	laevo-base	A M CH	>150 >150 >100	— — —	— — —	— — —	— — —

TABLE IV—continued
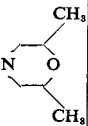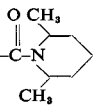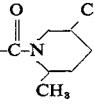
Serial number	R	α	β	NAA'	Salt	Animals*	ED50	L.L.	U.L.	S	f_s
R652	,,	H	CH₃	,, (N O with CH₃ groups)	base	A M CH	57·0 46·9 50·0	50·4 40·4 31·3	64·4 54·4 80·0	1·46 1·53 2·26	1·07 1·09 2·10
R822	,,	H	H	N O (CH₃, CH₃)	HCl	A M	63·0 69·8	53·8 60·7	73·7 80·3	1·50 1·43	1·15 1·12
R733	–C(=O)–N⟨	H	H	N(CH₃)₂	base	A M	>100 >100	— —	— —	— —	— —
R155	,,	H	H	N(iC₃H₇)₂	HCl	A M	>100 >25	— —	— —	— —	— —
R57 (ref. 15)	,,	H	H	N⟨	base	A M	>100 16·4	— 12·5	— 21·5	— 1·94	— 1·30
R550	,,	H	H	N O	,,	A M	73·0 87·5	62·9 79·6	84·7 96·3	1·40 1·23	1·24 1·05
R641	,,	CH₃	H	,,	,,	A M	59·0 77·0	53·9 68·1	64·6 87·0	1·33 1·37	1·13 1·20
R579	–C(=O)–N⟨ (O, CH₃)	H	H	,,	HCl H₂O	A M	>200 >200	— —	— —	— —	— —
R687	–C(=O)–N⟨ (O, CH₃, CH₃)	H	H	,,	base	A M	>100 >100	— —	— —	— —	— —
R601	–C(=O)–N⟨ (O, C₂H₅, CH₃)	H	H	,,	,,	A M	>100 87·5	— 74·2	— 103	— 1·31	— 1·18
R66	–C(=O)–N O	H	H	N(CH₃)₂	,,	A M	>200 >25	— —	— —	— —	— —
R74	,,	H	H	,,	CH₃I	A	>100	—	—	—	—
R73	–C(=O)–N O	H	H	N(C₂H₅)₂	HCl	A M	140 164	114 143	172 189	1·29 1·25	1·24 1·12
R149	,,	H	H	N(iC₃H₇)₂	base	A M	>100 >75	— —	— —	— —	— —
R147	,,	H	H	N⟨	,,	A M	>100 12·1	— 9·31	— 15·7	— 1·67	— 1·16
R152	,,	H	H	,,	CH₃I	A M	>100 >25	— —	— —	— —	— —
R151	,,	H	H	,,	C₂H₅Br	A M	>100 >25	— —	— —	— —	— —
R56	,,	H	H	N⟨	base	A M	>100 12·5	— 9·12	— 17·1	— 1·55	— 1·19
R144	,,	H	H	,,	CH₃I	A M	>100 >25	— —	— —	— —	— —
R67	,,	H	H	N O	base	A M	95·0 >25	89·6 —	100·7 —	1·12 —	1·10 —

TABLE IV—continued

Serial number	R	α	β	NAA'	Salt	Animals*	ED50	L.L.	U.L.	S	f_8
R628	$-\overset{O}{\overset{\|}{C}}$-N O (ring)	CH₃	·H	N O (ring)	base	A M	58.8 95.0	55.0 79.2	62.9 114	1.28 1.47	1.03 1.08
R642	,,	H	CH₃	,,	,,	A M	70.0 65.0	64.2 58.0	76.3 72.8	1.10 1.37	1.07 1.18
R64	$-\overset{O}{\overset{\|}{C}}$-OC₂H₅	H	H	N (ring)	C₂H₂O₄	A M	37.0 8.10	31.4 6.75	63.7 9.72	1.52 1.40	1.13 1.09
R609	,,	H	H	N O (ring)	base	A M	19.2 23.7	17.8 19.9	20.7 28.2	1.16 1.65	1.06 1.36
R934	,,	H	H	N (ring)	,,	A M	32.5 43.2	28.8 34.8	36.7 53.6	1.69 1.70	1.30 1.60
R618	$-\overset{O}{\overset{\|}{C}}$-CH₃	H	H	N O (ring)	HCl	A M	35.8 50.5	31.1 43.2	41.2 59.1	1.47 1.60	1.17 1.23
R743	$-\overset{O}{\overset{\|}{C}}$-C₂H₅	H	H	N(CH₃)₂	HCl	A M CH	11.6 13.2 18.3	10.3 12.3 14.4	13.1 14.1 23.2	1.55 1.22 1.31	1.20 1.04 1.27
Iso-meth-adone	,,	CH₃	H	,,	HCl H₂O	A M	7.90 10.0	7.12 9.00	8.77 11.1	1.52 1.50	1.10 1.10
Metha-done	,,	H	CH₃	,,	HCl	A M AO MO AR CH	5.18 4.75 26.5 34.1 4.90 4.85	4.80 4.48 21.5 27.5 3.92 2.98	5.59 5.04 32.6 42.3 6.13 7.91	1.53 1.23 1.79 1.92 1.55 2.23	1.19 1.04 1.42 1.49 1.40 2.08
R738	,,	H	H	N (ring)	base	A M	14.3 12.2	13.0 11.0	15.7 13.5	1.35 1.44	1.11 1.15
R892	,,	CH₃	H	,,	HBr ½ H₂O	A M	17.2 17.2	15.2 15.2	19.4 19.4	1.73 1.43	1.34 1.16
R833	,,	H	CH₃	,,	HCl	A M	6.82 7.09	6.14 6.39	7.57 7.87	1.58 1.53	1.20 1.18
R288	,,	H	H	N (ring)	HCl	A M CH	16.2 14.5 7.82	14.5 12.6 5.32	18.1 16.7 11.5	1.51 1.87 1.87	1.20 1.44 1.30
R836	,,	CH₃	H	,,	HCl	A M	12.8 15.9	10.9 14.2	15.1 17.8	1.80 1.38	1.36 1.12
R831	,,	H	CH₃	,,	HBr	A M	6.20 6.30	5.49 5.73	7.01 6.93	1.55 1.43	1.21 1.13
R607	,,	H	H	N O (ring)	base	A M	6.15 8.75	5.77 7.74	6.55 9.89	1.17 1.27	1.07 1.12
R783	,,	CH₃	H	,,	,,	A M	77.5 90.5	53.8 65.6	112 125	2.47 2.00	1.89 1.54
Phena-doxone	,,	H	CH₃	,,	HBr	A M AO MO AR CH	2.45 3.08 15.2 22.8 2.30 7.95	2.15 2.77 13.9 20.2 1.97 6.97	2.79 3.42 16.6 25.8 2.69 9.06	1.60 1.33 1.58 1.48 1.37 1.16	1.32 1.13 1.18 1.24 1.13 1.11
R770	,,	H	H	N(C₂H₅)₂	base	A M	30.9 35.8	24.1 29.1	39.6 44.0	1.88 1.33	1.27 1.11
R744	,,	H	H	N(nC₃H₇)₂	,,	A M	>100 >100	— —	— —	— —	— —
R294	,,	H	H	N(iC₃H₇)₂	HCl	A M	>200 >25	— —	— —	— —	— —

TABLE IV—*continued*
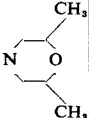
Serial number	R	α	β	NAA′	Salt	Animals*	ED50	L.L.	U.L.	S	f_g
R769	,,	H	H	$N(iC_4H_9)_2$	base	A M	>100 >100	— —	— —	— —	— —
R1052	,,	H	H	$N(CH_2)_6$	HCl	A M	16·8 11·6	13·9 9·83	20·3 13·7	1·85 1·45	1·46 1·22
R1093	,,	H	H	$N(CH_2)_7$	$C_2H_2O_4$	A M	>25 >25	— —	— —	— —	— —
R863	,,	H	H	N O (with CH₃, CH₃)	base	A M	140 176	94·0 135	209 229	2·20 1·45	1·67 1·18
R919	OH $-CH-C_2H_5$	CH_3	H	$N(CH_3)_2$	α-HCl	A M	32·1 55·0	28·2 43·3	36·6 70·0	1·49 2·12	1·22 1·99
R925	,,	H	CH_3	,,	,,	A M	37·0 33·0	31·4 38·0	43·7 38·9	1·58 1·31	1·24 1·13
R895	,,	H	CH_3	,,	β-HCl	A M	40·0 53·2	35·1 45·5	45·6 62·2	1·56 1·68	1·27 1·37
R1078	$O-COCH_3$ $-CH-C_2H_5$	H	CH_3	,,	α-(−)-HCl	A M	7·20 10·8	5·81 9·07	8·93 12·9	1·94 1·68	1·45 1·28
R1080	,,	H	CH_3	,,	α-(+)-HCl	A M	1·50 2·0	1·29 —	1·74 —	1·55 —	1·22 —
R1079	,,	H	CH_3	,,	β-(−)-HCl	A M	1·23 >1·5	1·02 —	1·49 —	1·80 —	1·60 —
R950	NH $-C-C_3H_5$	CH_3	H	$N(CH_3)_2$	2 HCl	A M	55·0 39·5	47·4 32·9	63·8 47·4	1·42 1·73	1·15 1·28
R878	,,	CH_3	H	$N(C_2H_5)_2$	2 HCl 3/2 H₂O	A M	>100 >100	— —	— —	— —	— —
R662	,,	CH_3	H	N O	base	A M	19·0 26·6	16·1 24·2	22·4 29·3	2·15 1·39	1·34 1·07
R832	,,	CH_3	H	N	2 HCl	A M	22·2 >25	17·0 —	29·1 —	2·33 —	1·48 —
R877	,,	CH_3	H	N	2 HCl H₂O	A M	61·0 37·3	41·5 27·8	89·7 50·0	2·23 1·60	1·90 1·34
R290	$N-COCH_3$ $-C-C_3H_5$	H	H	N (iC₃H₇, CH₃)	HCl	A	>200	—	—	—	—
R293	,,	H	H	$N(iC_3H_7)_2$	,,	A	>200	—	—	—	—
R247	,,	H	H	N	,,	A	>200	—	—	—	—
R916	,,	CH_3	H	$N(C_2H_5)_2$	,,	A M	>12·5 >12·5	— —	— —	— —	— —
R904	,,	CH_3	H	N	,,	A M	>25 >25	— —	— —	— —	— —
R835	,,	CH_3	H	N	,,	A M	37·9 47·3	33·0 43·2	43·6 53·0	1·55 1·43	1·27 1·16
R713	,,	CH_3	H	N O	,,	A M	7·10 8·90	6·17 7·95	8·17 9·97	1·97 1·60	1·35 1·19

TABLE IV—*continued*

	Ani-mals*	ED50	L.L.	U.L.	S	f_s
Morphine hydrochloride	A	12·0	11·2	12·8	1·69	1·08
	M	13·1	11·5	14·9	2·35	1·41
	AO	68·0	60·7	76·2	1·49	1·10
	MO	92·0	75·4	112·2	2·08	1·38
	AR	15·0	12·4	18·2	1·47	1·15
	CH	15·0	9·87	22·8	2·14	1·52
Morphine sulphate	A	10·5	9·38	11·8	1·66	1·33
Diacetylmorphine (heroin)	A	2·00	1·84	2·18	1·52	1·15
	M	2·03	1·85	2·24	1·59	1·17
	AR	1·00	0·85	1·17	1·20	1·12
	CH	10·8	6·39	18·3	2·79	2·03
Codeine phosphate	A	53·0	48·2	58·3	1·52	1·22
	M	70·0	61·4	79·8	1·58	1·32
	AR	142	118	170	1·45	1·20
	CH	32·5	20·3	52·0	2·16	1·98
Ethylmorphine HCl (Dionine)	A	55·8	45·7	68·1	1·75	1·26
	M	100	82·0	122	1·67	1·24
Levorphan	A	3·00	2·56	3·51	1·84	1·45
	M	2·94	2·21	3·91	2·98	2·25
Nalorphine HBr	A	>100	—	—	—	—
	M	>100	—	—	—	—
	AR	>75	—	—	—	—
Pethidine HCl	A	28·0	25·7	30·5	1·42	1·12
	M	21·5	19·5	23·7	1·27	1·07
	AO	65·5	59·5	72·1	1·35	1·14
	MO	69·5	62·1	77·8	1·41	1·18
	AR	54·5	45·0	66·0	1·45	1·21
	CH	56·0	38·1	82·3	1·56	1·40
N-Morpholino-ethyl-norpethidine 2 HCl (ref. 22)	A	18·6	15·0	23·1	2·14	1·46
	M	36·5	29·7	44·9	1·83	1·35
	AR	23·0	17·7	29·9	1·51	1·31
	CH	109·0	90·8	131	1·64	1·21
4-Carbethoxy-1-(2-hydroxy-2-phenethyl)-4-phenyl-piperidine HCl (ref. 27)	A	11·4	10·2	12·8	1·41	1·18
	M	14·4	12·6	16·4	1·59	1·30
	CH	36·0	24·2	53·6	1·92	1·64
1:1-(Di-2-thienyl)-3-(N-piperidino)-buten-1-ylamine HCl (ref. 22)	A	6·50	5·99	7·05	1·28	1·05
	M	6·40	5·82	7·04	1·42	1·10
	CH	18·9	15·2	23·4	1·41	1·32
Propoxyphene HCl (ref. 26)	A	65·8	57·7	75·0	1·34	1·09
	M	76·0	64·4	89·7	1·43	1·25
	CH	67·0	52·3	85·8	1·63	1·26
Atropine sulphate	A	>100	—	—	—	—
	M	0·096	0·084	0·109	1·40	1·10
	CH	16·5	11·8	23·1	6·14	1·99
Papaverine HCl	A	>100	—	—	—	—
	M	>100	—	—	—	—
	CH	95·0	73·6	123	2·19	1·33
Adiphenine HCl	A	>100	—	—	—	—
	M	47·8	41·6	55·0	1·43	1·22
	CH	>100	—	—	—	—

of this property and the analgesic activity in mice or rats (Fig. 6). The ED50 (charcoal) to ED50 (analgesia) ratio for methadone, morphine and codeine is not significantly different from one. Heroin, R 875 and its N-morpholino-analogues have a ratio of 5 to 10, whereas the N-piperidino-analogues of R 875 are surprisingly active in the charcoal-test (ratio of 0·2 to 0·6). Pethidine has a ratio of about 2.

It is reasonable to assume an inverse relation between ED50 (charcoal) to ED50 (analgesia) ratio and the constipating effect of analgesics.

R 875, the dextrorotatory isomer of (2:2-diphenyl-3-methyl-4 morpho-lino-butyryl-pyrrolidine (II), appears to be worth more investigation. It has twice the analgesic activity in mice and rats as the racemic mixture R 610 (the laevorotatory isomer, R 898, is inactive), and is more active than any other analgesic we have tested (Tables II and IV).

(II)
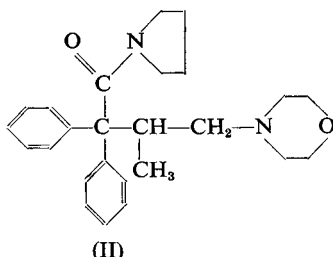
($\pm$)—R610.   (+)—R875.   (—)—R898.

SUMMARY

1.   Some pharmacological properties of a new series of secondary and tertiary basic amides are described.

2.   The relation between the analgesic activity in mice and rats, and the chemical structure of these amides is discussed.

3.   The *dextro*-rotatory isomer of 2:2-diphenyl-3-methyl-4-morpholino-butyrylpyrrolidine, R 875, is more active as an analgesic in mice and rats than any other compound tested.

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