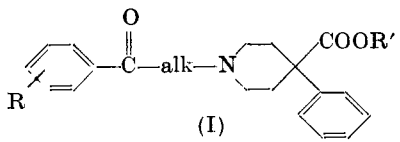
Journal of Medicinal and Pharmaceutical Chemistry

VOL. 2, No. 3 (1960)

Compounds Related to Pethidine—III. Basic Ketones derived from Norpethidine

PAUL A. J. JANSSEN, ANTON H. M. JAGENEAU, PAUL J. A. DEMOEN, CORN. VAN DE WESTERINGH, JULIENNE H. M. DE CANNIÈRE, ALFONS H. M. RAEYMAEKERS, MARIA S. J. WOUTERS, STEFAN SANCZUK and BERT K. F. HERMANS, *Research Laboratories Dr. C. Janssen, Beerse (Turnhout), Belgium*

A further step in our studies on compounds derived from norpethidine-type esters, was the investigation of compounds of general structure (I).



(I)

As in Part II, R is any substituent, and R' an unsubstituted alkyl or aralkyl-group; 'alk' stands for any branched or unbranched carbon chain other than $—CH_2CH_2—$.

Synthesis

The methods of preparing 39 compounds of this series are summarized by the following reaction schemes; the intermediate ketones are described in the literature and the preparation of the norpethidine-type esters has been recorded in Part II.[2]

I. Condensation of the appropriate haloalkaryl-ketone with the norpethidine-like ester.

All but three compounds were synthesized by this method, as follows:

1. Two moles of the appropriate secondary amine were heated

with one mole of haloketone in an inert solvent. The reaction times and temperatures were dependent on the reactivity of the haloketone, varying from 10 min at reflux-temperature in ether for the very reactive phenacyl bromides, to 2 or 3 days in a sealed tube in toluene at 140–150° for the less reactive chlorobutyro- and chlorovalerophenones.

2. Equimolar quantities of the reactants dissolved in methyl-isobutyl ketone or *n*-butanol were heated under reflux in the presence of an organic or inorganic base, usually sodium carbonate. Potassium iodide was added for the activation of the haloketone.

II. Mannich reaction involving propiophenone or desoxybenzoin, the hydrochloride of the norpethidine-like ester and paraformaldehyde.

III. Addition of the norpethidine-like ester to crotonophenone.

Examples

1. *Synthesis of 4-[1-(4-carbethoxy-4-phenyl)piperidine]-butyrophenone hydrochloride (R 1187).* A solution of 4-chlorobutyrophenone (8 g), norpethidine (11 g) and potassium iodide (0·1 g) in dry xylene (100 ml) was heated in a sealed tube at 100° for 35 h. After cooling, the reaction mixture was filtered, the filtrate extracted with water (50 ml) and dried over anhydrous potassium carbonate. After filtration, the solvent was distilled off under reduced pressure and the residue dissolved in ether (200 ml). Dry hydrochloric acid was passed through the solution and the precipitated salt was recrystallized from isopropanol to yield the *hydrochloride* (R 1187) (24 per cent), (m.p. 135–136°).

2. *Synthesis of 2-[1-(4-carbethoxy-4-phenyl)piperidine]-propiophenone hydrochloride (R 1204).* Norpethidine (10·2 g, 0·05 M) dissolved in anhydrous ether (30 ml) was added to 2-bromopropiophenone (5·3 g, 0·025 M), dissolved in anhydrous ether (20 ml).

Norpethidine hydrobromide precipitated instantaneously; the mixture was refluxed for 10 min, and the solid residue filtered off and washed with anhydrous ether. The ethereal extract was dried with potassium carbonate, filtered and the gaseous HCl passed through the solution. After evaporation under reduced

pressure, a gel-like mass was obtained; this was dissolved in chloroform, and ether and acetone added until turbidity resulted. The *hydrochloride* (R1204) (2·2 g) crystallized on standing the solution at −15°; m.p. 98–100°.

3. *Synthesis of 3-[1-(4-carbethoxy-4-phenyl)piperidine]-isobutyrophenone (R 960).* Propiophenone (3 g), norpethidine hydrochloride (5 g), paraformaldehyde (0·9 g) and one drop of hydrochloric acid were dissolved in isopropanol (30 ml).

After refluxing the solution for one hour, more paraformaldehyde (0·6 g) was added and refluxing was continued for 2 h. The base was liberated with alkali and recrystallized from ether isopropanol to yield 1·5 g of the base R960; m.p. 107·6–110·6°.

4. *Preparation of 3-[1-(4-carbethoxy-4-phenyl)piperidine]butyrophenone hydrochloride (R1133).* Norpethidine (24·5 g, 0·15 M) was dissolved in toluene (100 ml), and crotonophenone (14·6 g, 0·10 M) was added with stirring at 10° C. After the addition was completed, stirring was continued for 4 h, keeping the internal temperature at 35–40°.

The reaction mixture was then allowed to stand overnight at room temperature and extracted with dilute hydrochloric acid. The aqueous layer was made alkaline with dilute ammonia and the liberated oil extracted with ether. The ethereal solution was dried over Na_2SO_4 (anhyd.), filtered and saturated with gaseous hydrochloric acid. The precipitated hydrochloride was recrystallized from isopropanol to yield the pure *hydrochloride* (R1133) (27 g); m.p. 135·6–136·8°.

The analytical data for the compounds of general structure (I) are recorded in Table I.

Pharmacology

The pharmacological methods have been described previously;[1] the results are summarized in Table II. The influence of the size of the carbon chain in (I) on certain biological activities is presented in Table III. Serial number R951, discussed in Part I,[1] (I; R = H, R′ = C_2H_5, alk = —CH_2CH_2—) is included for reference.

Table I. Analytical data of the aralkyl-ketones of the norpethidine-like esters (I)

	Serial number	R	R′	—alk—	Formula	m.p., °C	Equiv. wt.		% Cl		λ (mμ)	$\epsilon \times 10^{-3}$	Method of synth.
							Calcd.	Found	Calcd.	Found			
1	R 992	H	C_2H_5	—CH_2—	$C_{22}H_{25}NO_3$	113·0–4·5	351·4	345	—	—	241	12·3	I
2	R 1153	2,5-$(CH_3)_2$	C_2H_5	—CH_2—	$C_{24}H_{29}NO_3$.HCl	171·6–2·4	416·0	410	8·52	8·59	251	10·6	I
3	R 1399	3-OCH_3	C_2H_5	—CH_2—	$C_{23}H_{27}NO_4$.HCl	148–52	417·9	415	8·48	8·90	255	6·6	I
4	R 1338	H	CH_3	—$CH_2CH_2CH_2$—	$C_{23}H_{27}NO_3$.HCl	201·5–2·5	401·9	402	8·82	8·82	244	13·7	I
5	R 1187	H	C_2H_5	,,	$C_{24}H_{29}NO_3$.HCl	135–6	415·9	414	8·52	8·64	243	13·5	I
6	R 2008	H	C_3H_5	,,	$C_{25}H_{29}NO_3$	66·5–67	391·4	392	[a]	—	245	14·2	I
7	R 1332	H	*n*-C_3H_7	,,	$C_{25}H_{31}NO_3$.HCl	118·5–20·2	430·0	431	8·25	8·17	244	13·2	I
8	R 1328	H	iso-C_3H_7	,,	$C_{25}H_{31}NO_3$.HCl	146–9·2	430·0	437	8·25	8·23	243	13·3	I
9	R 1855	H	*n*-C_4H_9	,,	$C_{26}H_{33}NO_3$.HCl	133·6–5·2	444·0	448	7·99	8·09	244	12·8	I
10	R 1888	H	*sec*-C_4H_9	,,	$C_{26}H_{33}NO_3$.HCl	139·8–40·4	444·0	445	7·99	7·89	245	13·2	I
11	R 1826	H	*n*-C_5H_{11}	,,	$C_{27}H_{35}NO_3$.HCl	122·4–4·2	458·0	454	7·74	7·70	244	12·8	I
12	R 1842	H	C_6H_{11}	,,	$C_{28}H_{35}NO_3$.HCl	141–2	470·0	468	7·54	7·55	245	13·1	I
13	R 1884	H	$CH_2CH_2C_6H_5$	,,	$C_{30}H_{33}NO_3$	85·5–6·5	455·6	458	[b]	—	245	13·9	I
14	R 1830	4-F	CH_3	,,	$C_{23}H_{26}FNO_3$.HCl	182–3·6	419·9	417	8·44	8·54	246	12·2	I
15	R 1823	4-F	C_2H_5	,,	$C_{24}H_{28}FNO_3$.HCl	130·6–32	433·9	436	8·19	8·19	246	12·1	I
16	R 1893	4-F	*n*-C_3H_7	,,	$C_{25}H_{30}FNO_3$.HCl	128·8–9·8	448·0	449	7·91	7·83	247	12·5	I
17	R 1849	4-F	iso-C_3H_7	,,	$C_{25}H_{30}FNO_3$.HCl	165·8–7	448·0	447	7·91	7·96	247	12·5	I
18	R 1848	4-Cl	CH_3	,,	$C_{23}H_{26}ClNO_3$.HCl	196–6·8	436·4	432	8·13	8·05	254	15·8	I

19	R 1880	4-Cl	C_2H_5	,,	$C_{24}H_{28}ClNO_3.HCl$	167·4–8·8	450·4	452	7·88	7·87	254	16·9	I
20	R 1858	4-Cl	n-C_3H_7	,,	$C_{25}H_{30}ClNO_3.HCl$	127·2–8·4	464·4	468	7·64	7·54	254	18·0	I
21	R 1881	4-Cl	iso-C_3H_7	,,	$C_{25}H_{30}ClNO_3.HCl$	183–3·5	464·4	469	7·64	7·69	254	17·7	I
22	R 1828	4-CH_3	CH_3	,,	$C_{24}H_{29}NO_3.HCl$	188–8·6	415·9	413	8·52	8·53	255	15·9	I
23	R 1889	4-CH_3	C_2H_5	,,	$C_{25}H_{31}NO_3.HCl$	160–1·5	430·0	436	8·25	8·32	255	15·2	I
24	R 1965	4-CH_3	n-C_3H_7	,,	$C_{26}H_{33}NO_3$	56·6–8·4	407·5	410	[e]	—	256	16·2	I
25	R 1882	4-CH_3	iso-C_3H_7	,,	$C_{26}H_{33}NO_3.HCl$	168·5–9·5	440·0	446	7·99	8·09	256	15·9	I
26	R 1836	4-OCH_3	CH_3	,,	$C_{24}H_{29}NO_4.HCl$	203·5–4·5	431·9	431	8·21	8·20	276	14·9	I
27	R 1863	4-OCH_3	C_2H_5	,,	$C_{25}H_{31}NO_4$	83·5–4·2	409·5	406	[d]	—	277	17·1	I
28	R 2010	4-OCH_3	C_2H_5	,,	$C_{25}H_{31}NO_4.HCl$	128·6–30·4	446·0	442	7·95	8·04	277	16·2	I
29	R 1930	4-OCH_3	n-C_3H_7	,,	$C_{26}H_{33}NO_4$	65–6	423·5	431	[e]	—	278	17·1	I
30	R 1887	4-OCH_3	iso-C_3H_7	,,	$C_{26}H_{33}NO_4$	93–4	423·5	421	[f]	—	278	16·2	I
31	R 1919	H	CH_3	—$CH_2CH_2CH_2CH_2$—	$C_{24}H_{29}NO_3.HCl$	185–6·5	415·9	413	8·52	8·51	244	15·0	I
32	R 1336	H	C_2H_5	,,	$C_{25}H_{31}NO_3.HCl$	179–80	430·0	426	8·25	8·17	243	12·4	I
33	R 1920	H	n-C_3H_7	,,	$C_{26}H_{33}NO_3.HCl$	154·5–5·5	444·0	444	7·99	7·99	244	15·6	I
34	R 1924	H	iso-C_3H_7	,,	$C_{26}H_{33}NO_3.HCl$	178·4–9·4	444·0	442	7·99	8·00	244	13·6	I
35	R 1723	4-Cl	C_2H_5	,,	$C_{25}H_{30}ClNO_3.HCl$	167–8	464·4	467	7·64	7·59	254	17·0	I
36	R 1204	H	C_2H_5	—$CH(CH_3)$—	$C_{23}H_{27}NO_3.HCl$	98–100	401·9	400	8·82	8·81	252	10·3	I
37	R 960	H	C_2H_5	—$CH(CH_3)CH_2$—	$C_{24}H_{29}NO_3$	107·6–10·6	379·5	385	[g]	—	242	11·1	II
38	R 1133	H	C_2H_5	—$CH_2CH(CH_3)$—	$C_{24}H_{29}NO_3.HCl$	135·6–6·8	415·9	420	8·52	8·56	244	13·3	III
39	R 973	H	C_2H_5	—$CH(C_6H_5)CH_2$—	$C_{29}H_{31}NO_3$	123–4	441·6	447	[h]	—	244	12·6	II

[a] N: Calcd., 3·58; found, 3·64.
[b] N: Calcd., 3·07; found, 2·99.
[c] N: Calcd., 3·44; found, 3·42.
[d] N: Calcd., 3·42; found, 3·48.
[e] N: Calcd., 3·31; found, 3·38.
[f] N: Calcd., 3·31; found, 3·43.
[g] N: Calcd., 3·70; found, 3·60.
[h] N: Calcd., 3·17; found, 3·25.

Table II. Pharmacological results

	Serial number	Test[a]	ED_{50} mg/kg	L.L.[b]	U.L.	S[b]	f_S[b]	Number of animals
1	R 992	A.M.	> 80	—	—	—	—	30
		M.M.	> 80	—	—	—	—	30
		CH	18	14	23	1·8	1·4	50
2	R 1153	A.M.	> 80	—	—	—	—	15
		M.M.	> 80	—	—	—	—	15
		CH	33	23	46	3·0	1·7	80
3	R 1399	A.M.	> 80	—	—	—	—	30
		M.M.	> 80	—	—	—	—	30
4	R 1338	A.M.	2·6	2·3	2·9	1·5	1·1	190
		M.M.	> 10	—	—	—	—	190
5	R 1187	A.M.	2·5	2·2	2·9	1·5	1·1	90
		M.M.	7·3	4·5	12	1·8	1·5	90
		A.R.	3·1	2·8	3·4	1·6	1·1	190
		CH	17	14	21	1·3	1·1	59
6	R 2008	A.M.	5·3	3·5	8·1	2·3	1·4	60
		M.M.	> 40	—	—	—	—	60
7	R 1332	A.M.	7·0	5·6	8·7	2·2	1·3	135
		M.M.	> 25	—	—	—	—	135
8	R 1328	A.M.	6·7	5·2	8·6	3·2	1·4	179
		M.M.	> 25	—	—	—	—	179
9	R 1855	A.M.	> 40	—	—	—	—	10
		M.M.	> 40	—	—	—	—	10
10	R 1888	A.M.	> 40	—	—	—	—	30
		M.M.	> 40	—	—	—	—	30
11	R 1826	A.M.	> 40	—	—	—	—	10
		M.M.	> 40	—	—	—	—	10
12	R 1842	A.M.	> 40	—	—	—	—	10
		M.M.	> 40	—	—	—	—	10
13	R 1884	A.M.	> 40	—	—	—	—	30
		M.M.	> 40	—	—	—	—	30
14	R 1830	A.M.	1·6	1·1	2·5	1·9	1·3	55
		M.M.	> 40	—	—	—	—	55
		CH	4·2	2·9	6·1	2·7	1·5	70
15	R 1823	A.M.	1·9	1·3	2·8	2·4	1·5	80
		M.M.	> 40	—	—	—	—	80
16	R 1893	A.M.	3·1	1·8	5·0	2·2	1·4	50
		M.M.	> 40	—	—	—	—	50
17	R 1849	A.M.	2·9	2·0	4·3	1·8	1·2	50
		M.M.	> 40	—	—	—	—	50
18	R 1848	A.M.	> 40	—	—	—	—	10
		M.M.	> 40	—	—	—	—	10

[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.).

	Serial number	Test[a]	ED_{50} mg/kg	L.L.[b]	U.L.[b]	S[b]	fs[b]	Number of animals
19	R 1880	A.M.	> 80	—	—	—	—	30
		M.M.	> 80	—	—	—	—	30
20	R 1858	A.M.	> 40	—	—	—	—	40
		M.M.	> 40	—	—	—	—	40
21	R 1881	A.M.	> 80	—	—	—	—	30
		M.M.	> 80	—	—	—	—	30
22	R 1828	A.M.	> 40	—	—	—	—	10
		M.M.	> 40	—	—	—	—	10
23	R 1889	A.M.	> 40	—	—	—	—	30
		M.M.	> 40	—	—	—	—	30
24	R 1965	A.M.	> 40	—	—	—	—	20
		M.M.	> 40	—	—	—	—	20
25	R 1882	A.M.	> 80	—	—	—	—	30
		M.M.	> 80	—	—	—	—	30
26	R 1836	A.M.	> 40	—	—	—	—	10
		M.M.	> 40	—	—	—	—	10
27	R 1863	A.M.	> 40	—	—	—	—	10
		M.M.	> 40	—	—	—	—	10
29	R 1930	A.M.	> 40	—	—	—	—	20
		M.M.	> 40	—	—	—	—	20
30	R 1887	A.M.	> 80	—	—	—	—	30
		M.M.	> 80	—	—	—	—	30
31	R 1919	A.M.	17	11	26	1·9	1·4	40
		M.M.	40	32	50	1·3	1·1	40
32	R 1336	A.M.	10	7·9	13	2·3	1·5	105
		M.M.	18	14	23	2·0	1·4	105
33	R 1920	A.M.	> 40	—	—	—	—	20
		M.M.	> 40	—	—	—	—	20
34	R 1924	A.M.	> 40	—	—	—	—	20
		M.M.	> 40	—	—	—	—	20
35	R 1723	A.M.	> 40	—	—	—	—	10
		M.M.	> 40	—	—	—	—	10
36	R 1204	A.M.	> 50	—	—	—	—	15
		M.M.	> 50	—	—	—	—	15
37	R 960	A.M.	21	19	24	1·4	1·1	90
		M.M.	27	24	31	1·3	1·1	90
		CH	> 50	—	—	—	—	20
38	R 1133	A.M.	14	12	17	1·9	1·2	160
		M.M.	30	24	37	2·4	1·4	160
39	R 973	A.M.	> 100	—	—	—	—	20
		M.M.	> 100	—	—	—	—	20
		CH	46	33	64	1·9	1·6	39

[b] L.L. and U.L.: lower and upper fiducial limits ($P = 0{\cdot}05$).
S: slope.
fs: factor for computing confidence limits ($P = 0{\cdot}05$).

Table III. Structure (I): R = H; R′ = C_2H_5

The effect of varying the carbon chain 'alk' on compounds of type I: R = H, R′ = C_2H_5

—alk—	ED_{50} values in μmol/kg S.C.		
	analgesia	mydriasis	charcoal test
—CH_2—	> 180	> 180	51
—CH_2CH_2—	1·1	1·9	11
—$CH_2CH_2CH_2$—	6·1	18	41
—$CH_2CH_2CH_2CH_2$—	23	43	—
—$CH(CH_3)$—	> 125	> 125	—
—$CH_2CH(CH_3)$—	35	72	—
—$CH(CH_3)CH_2$—	57	72	> 130
—$CH(C_6H_5)CH_2$—	> 180	> 180	104

Consideration of the Pharmacological Results

In the present note, only broad generalizations are made.

1. Shortening of the two carbon chain, 'alk' in (I), results in a complete loss of both the analgesic and mydriatic activities. The inhibitory effect in the charcoal meal test is reduced to 1/5. Substitution of the ketonic phenyl ring [3-OCH_3 or 2,5-$(CH_3)_2$] fails to increase activity.

2. Lengthening of the two carbon chain, 'alk' in (I), progressively decreases analgesic and mydriatic potency of the unsubstituted propiophenones. In view of the previous results in the propiophenone series (Parts I[1] and II[2]) the inactivity of butyrophenones, substituted in the ketonic phenyl ring with chlorine, methoxy or methyl, was to be expected.

The pharmacological properties of the basic esters obtained by *para* fluoro-substitution of the butyrophenone derivatives (I; R = 4-F; alk = $CH_2CH_2CH_2$) are of interest. These fluorobutyrophenones, which are nearly devoid of mydriatic activity, are somewhat more active in the hot plate test than the corresponding unsubstituted butyrophenones. Their M.M.: A.M. ratios are much larger (> 10) than those of all morphine-like analgesics

tested in this laboratory.[3] In contrast with previously described series of esters related to pethidine, the influence of variations in the ester function (CH_3, C_2H_5, C_3H_7 and iso-C_3H_7) of these *para* fluoro-substituted butyrophenone derivatives on activity in the hot plate test is small (see Table IV). The 'analgesic' activity

Table IV. The effect of varying the ester function, COOR', in compounds of type I

Compd. I	alk = —CH_2CH_2—						alk: —$CH_2CH_2CH_2$—					
R	H			4–F			H			4–F		
R'	M.M.	A.M.	ratio	M.M.	A.M.	ratio	M.M.	A.M.	ratio	M.M.	A.M.	ratio
CH_3	6·0[a]	2·6	2·3	27	13	2·1	25	6·5	3·8	>90	3·8	>23
C_2H_5	1·9	1·1	1·7	11	2·6	4·2	18	6·0	3·0	>90	4·4	>20
iso-C_3H_7	9·7	6·1	1·6	>180	85	>2·0	>50	16	>3·0	>90	6·5	>13
n-C_3H_7	109	66	1·6	—	—	—	>50	16	>3·0	>90	6·9	>13

[a] ED_{50}-values for analgesic activity in μmol/kg S.C.

of these compounds is less antagonized by nalorphine than the analgesic activities of classical morphine-like analgesics (unpublished data). It may be concluded that introduction of a *para* fluoro-substituent in the ketonic phenyl ring of 4-(4-carbalkoxy-4-phenyl-piperidino)-butyrophenones (I; alk = $CH_2CH_2CH_2$) leads to a series of potent CNS depressing agents which are not to be regarded as typical morphine-like analgesics.

3. Branching of the carbon chain, 'alk', in (I) with methyl or phenyl groups, lowers activity. No marked difference is noted between the activity of the isobutyrophenone and the 3-butyrophenone-derivatives.

Summary. Shortening, lengthening or branching of the nitrogen-carbonyl alkyl bridge in 3-[1-(4-carboxy-4-phenyl)piperidine]-propiophenones, results in decreased activity.

Introduction of a *para* fluoro-substituent in the corresponding butyrophenone-derivatives confers CNS activities other than analgesic activities on the compounds.

(*Revised MS received 1 February, 1960*)

References

[1] Janssen, Paul A. J. *et al.* This Journal, **1**, 105 (1959)
[2] Janssen, Paul A. J. *et al.* This Journal, **1**, 309 (1959)
[3] Janssen, Paul A. J. and Jageneau, A. *Experientia*, **12**, 293 (1956)