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Compounds Related to Pethidine

I. Arylcarbamoylalkyl- and 3-Arylamino-2-hydroxypropyl Derivatives of Norpethidine and 4-Hydroxy-4-phenylpiperidine

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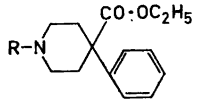
A number of compounds in which the nitrogen of norpethidine and of 4-hydroxy-4-phenylpiperidine is linked to an aniline residue over an acyl or a 2-hydroxypropyl bridge were prepared and tested for analgesic and central depressing activity. One such compound, β-(4-ethoxycarbonyl-4-phenylpiperidino)-propionanilide, was as active as morphine in the analgesic test.

Pethidine (I, R = CH_3) was synthesised by Eisleb [1] as a potential spasmolytic drug; its analgesic properties was discovered by Schaumann [2] in 1939, as it caused the characteristic Straub reaction when given to mice.



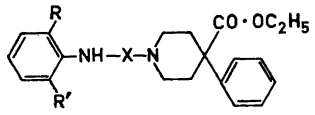
I

It was thought for some years that optimal effect was obtained with a methyl substituent at the nitrogen, but it was later found that if the N-methyl group was replaced by groups such as aralkyl [3–5], *tert.* aminoalkyl [6], alkoxyalkyl [7], aryloxyalkyl [8], arylaminoalkyl [9], phenyloxoalkyl [10], or 3-aryloxy-2-hydroxypropyl [11], the analgesic activity was considerably enhanced.

The present paper describes the synthesis of some related compounds, in which the nitrogen in norpethidine is linked to an anilino residue over an acyl (I, R = Ar—NH—CO-alkyl-) or a 2-hydroxypropyl (I, R = Ar—NH—CH_2—CHOH—CH_2—) bridge.

The so-called "reversed esters" of pethidine, *i.e.* N-methyl-4-acyloxy-4-phenylpiperidine (II) and related compounds are also potent analgesics [12],

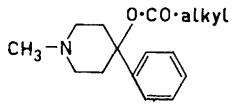
Table 1.



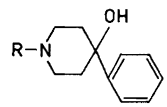
No.	R	R′	X	Yield %	Derivative	M.p. °C	Recryst. solvent[a]	Formula	Calc. %			Found %		
									C	H	N	C	H	N
1	H	H	$-CO\cdot CH_2-$	83	HCl	178–180 (dec.)	M–Et	$C_{22}H_{26}N_2O_3\cdot HCl$	65.6	6.76	6.95	65.3	6.76	6.75
					Base	73– 75	L	$C_{22}H_{26}N_2O_3$	72.1	7.15	7.65	72.4	6.99	8.00
2	CH_3	CH_3	»	58	HCl	120–122	M–Et	$C_{24}H_{30}N_2O_3\cdot HCl$	66.9	7.25	6.50	66.3	7.20	6.41
					Base	115–116	P	$C_{24}H_{30}N_2O_3$	73.1	7.67	7.10	72.9	7.48	6.95
3	H	H	$-CO\cdot CH_2\cdot CH_2-$	32	HCl	200–202	M–Et	$C_{23}H_{28}N_2O_3\cdot HCl$	66.3	7.01	6.72	65.8	7.01	6.87
4	CH_3	CH_3	$-CH_2\cdot CH(OH)\cdot CH_2-$	62	2 HCl	152–154	E–Et	$C_{25}H_{34}N_2O_3\cdot 2HCl$	62.1	7.51	5.80	61.5	7.43	5.45
5	CH_3	Cl	»	66	2 HCl	148–150	E–Et	$C_{24}H_{31}ClN_2O_3\cdot 2HCl$	57.2	6.60	5.56	56.5	6.78	5.34

[a] Ac, acetone; E, ethanol; Et, ether; L, ligroin; M, methanol; P, petroleum ether; X, xylene.

and it was recently reported [13] that butyrophenone derivatives of the parent alcohol, 4-hydroxy-4-phenylpiperidine, (III, R = Ar—CO—$(CH_2)_3$—) have tranquillising properties. One member of this series (γ-[4-(*p*-chlorophenyl)-4-hydroxypiperidino]-*p*-fluorobutyrophenone, haloperidol) has found widespread clinical use.



II



III

It was interesting to attach to the piperidine nitrogen of this type of compound, derived from 4-hydroxy-4-phenylpiperidine, substituents that were similar to those we used in the preparation of the substituted pethidines.

A number of (4-hydroxy-4-phenylpiperidino)-acylanilines (III, R = Ar—NH—CO-alkyl-) and 1-arylamino-3-(4-hydroxy-4-phenylpiperidino)-2-propanols (III, R = Ar—NH—CH_2—CHOH—CH_2—) were therefore prepared and tested.

The new compounds (see Tables 1 and 2) were obtained by reacting ethyl 4-phenylpiperidine-4-carboxylate or 4-hydroxy-4-phenylpiperidine with a halogenoacylaniline or a N-(2,3-epoxypropyl)-aniline, respectively.

After the experimental work was completed compounds 6 and 8 in Table 2 were described in U.S.P. 2,937,181 (P. A. J. Janssen).

Pharmacology. Analgesia in mice was tested by a modification of the method of Haffner [14,15]. A bulldog clamp with thin rubber-covered tips was applied at the root of the tail. If the mouse did not react to the stimulus within thirty seconds the test was considered positive. The substances were given intraperitoneally to five mice thirty minuters before testing. The analgesic effect of the substances was compared to that of codeine phosphate.

Several of the substances were tested for their possible effect upon the conditioned reflex response in rats. The conditioned reflex was evoked by a sound signal (buzzer) and the unconditioned reflex by an electric shock. The blocking of the conditioned response without effect on the unconditioned response was taken as a measure of the tranquillising effect. Chloropromazine was used as standard.

The antagonism of the substances to amphetamine hyperactivity in mice was used as a measure of sedative or tranquillising effect. The substances were given intraperitoneally to groups of five mice thirty minutes before dosing i.p. with 20 mg/kg of (+)-amphetamine sulphate. The degree of hyperactivity was observed 45 min. later. Also in this test the effect was compared to that of chloropromazine.

β-(4-Ethoxycarbonyl-4-phenylpiperidino)-propionanilide (No. 3 in Table 1) had an analgesic activity eight times that of codeine phosphate, which was of the same order as that of morphine on our strain of mice, and was the only compound that exceeded the standard in activity. It had the same activity as chloropromazine on the conditioned reflex response. Addiction to this compound seems to take place in rats as the amount of the substance necessary to block the conditioned response increased upon repeated injections after some days' interval.

Table 2.

No.	R	R′	X	Yield %	Deriva-tive	M.p. °C	Recryst. solvent[a]	Formula	Calc. %			Found %		
									C	H	N	C	H	N
6	H	H	$-CO\cdot CH_2-$	53	HCl	212–214	Ac–Et	$C_{19}H_{22}N_2O_2\cdot HCl$	65.8	6.69	8.08	65.8	6.82	8.05
					Base	120–121	P–Et	$C_{19}H_{22}N_2O_2$	73.5	7.15	9.03	72.8	6.82	8.74
7	CH_3	CH_3	»	57	HCl	157–160	E–Et	$C_{21}H_{26}N_2O_2\cdot HCl$	67.3	7.26	7.47	67.0	7.39	7.16
					Base	142–143	P	$C_{21}H_{26}N_2O_2$	74.5	7.74	8.28	74.5	7.63	7.93
8	H	H	$-CO\cdot CH_2\cdot CH_2-$	62	HCl	205–207 (dec.)	M–Et	$C_{20}H_{24}N_2O_2\cdot HCl$	66.6	6.98	7.76	66.0	6.72	7.94
					Base	130–131	P	$C_{20}H_{24}N_2O_2$	74.0	7.46	8.64	73.8	7.53	8.79
9	CH_3	CH_3	$-CH_2\cdot CH(OH)\cdot CH_2-$	69	2 HCl	212–213	M–Et	$C_{22}H_{30}N_2O_2\cdot 2HCl$	61.8	7.55	6.56	61.6	7.89	6.62
10	CH_3	Cl	»	52	Base	131–132	X–Et	$C_{22}H_{30}N_2O_2$	74.5	8.53	7.91	74.6	8.64	8.08
					2 HCl	174–175 (dec.)	M–Et	$C_{21}H_{27}ClN_2O_2\cdot 2HCl$	56.3	6.53	6.26	56.4	6.40	6.51
					Base	150–151	P–Et	$C_{21}H_{27}ClN_2O_2$	67.3	7.26	7.47	67.0	7.17	7.82

[a] See Table 1.

EXPERIMENTAL

Ethyl 4-phenylpiperidine-4-carboxylate (norpethidine; I, R = H) was prepared as described by Eisleb [1]: N-Bis-(β-chloroethyl)-*p*-toluenesulphonamide was caused to react with benzyl cyanide in the presence of sodium amide, and the product of reaction hydrolysed and esterified. We found that the yields could be improved considerably by using sodium hydride in dimethylformamide instead of sodium amide in toluene.

4-Phenylpiperidine-4-ol [13], *N-(2,3-epoxypropyl)-2,6-dimethylaniline* [16] and *N-(2,3-epoxypropyl)-2-chloro-6-methylaniline* [16] were prepared according to procedures described in the literature.

(4-Ethoxycarbonyl-4-phenylpiperidino)-acylanilines. A mixture of ethyl 4-phenylpiperidine-4-carboxylate (0.03 mole), the appropriate halogenoacylaniline (0.03 mole), anhydrous potassium carbonate (0.1 mole) and toluene (100 ml) was heated with vigorous stirring at a bath temperature of 120° until the evolution of carbon dioxide ceased (4—7 h). After cooling, the reaction mixture was filtered and the hydrochloride af the reaction product was precipitated by addition of ethereal hydrogen chloride. The salt was purified by recrystallisation.

(4-Hydroxy-4-phenylpiperidino)-acylanilines. These compounds were prepared by the same method from 4-hydroxy-4-phenylpiperidine and the appropriate halogenoacylaniline.

1-Arylamino-3-(4-ethoxycarbonyl-4-phenylpiperidino)-2-propanols. A solution of ethyl 4-phenylpiperidine-4-carboxylate (0.03 mole) and the appropriate N-(2,3-epoxypropyl)-aniline (0.03 mole) in xylene (25 ml, mixture of isomers of b.p. 138—142°) was refluxed for 8 h. The product was isolated and purified as described for the previous compounds.

1-Arylamino-3-(4-hydroxy-4-phenylpiperidino)-2-propanols. These compounds were prepared by the same method from 4-hydroxy-4-phenylpiperidine and the appropriate N-(2,3-epoxypropyl)-aniline.

Physical constants and analytical data are collected in Tables 1 and 2.

The compounds were dried at 50° and 0.05 mm before analysis. The analyses were performed by Dr. A. Bernhardt, Mülheim, Germany.

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