114. *Search for New Analgesics. Part II. Further Homologues of Pethidine and the Pharmacology of these and other Compounds.*

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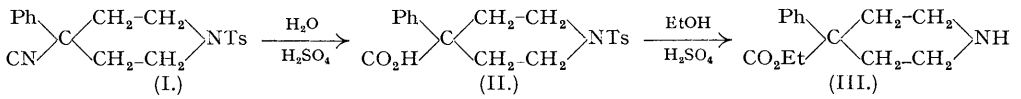
This paper describes the preparation of norpethidine by route (I) —> (II) —> (III), and its alkylation to *N*-methyl (pethidine), *N*-ethyl, *N*-*n*-propyl, N-n-iso*propyl*, *N*-*n*-butyl, N-sec.-*butyl*, N-n-*amyl*, N-1-*methylbutyl*, and N-*allyl* derivatives.

The toxic, spasmolytic, and analgesic activity of these compounds and of a number of related lactones and pyrrolidones, described in Part I (*loc. cit.*), is also discussed.

Following the discovery of pethidine (Eisleb and Schaumann, *Deut. med. Woch.*, 1939, **65**, 967), the pharmacology, but not the chemistry, of a considerable number of its derivatives, including some *N*-alkyl homologues, has been described by Schaumann (*Arch. exp. Path. Pharm.*, 1940, **196**, 109) and by Eisleb (*Medizin u. Chemie*, 1942, **213**). Before these results were fully available in this country, however, we prepared a short series of *N*-alkyl homologues of pethidine, some of which have not apparently been examined by the German workers. A few of these compounds had previously been synthesised by ring closure of ethyl αα′-bis-(β′-bromoethyl)phenylacetate with the appropriate primary amine (Walton and Green, Part I, *J.*, 1945, 315), but in general it was found more convenient to prepare the required homologues by *N*-alkylation of norpethidine (III).



Norpethidine was originally obtained by Eisleb in two ways: (*a*) from 4-cyano-1-benzyl-4-phenylpiperidine by hydrolysis and esterification followed by debenzylation (B.P. 501,135), and (*b*) from 4-cyano-1-*p*-tosyl-4-phenylpiperidine (I) by combined hydrolysis and esterification using sulphuric acid (*Ber.*, 1941, **74**, 1446). The latter process has now been examined in more detail. Treatment of the cyanide (I) with moderately concentrated sulphuric acid failed to remove the tosyl group, but gave 1-p-*tosyl*-4-*phenylpiperidine*-4-*carboxylic acid* (II) in good yield. On the other hand, the tosyl group was readily removed from the acid (II) by alcoholysis yielding norpethidine, which was readily isolated in the form of its carbonate. Preliminary attempts to bring about direct alcoholysis of the cyanide (I) were unsuccessful, owing to its comparative insolubility in alcohol.

Norpethidine was alkylated in the usual manner to give its *N*-methyl, *N*-ethyl, *N*-*n*-propyl, N-iso*propyl*, *N*-*n*-butyl, N-sec.-*butyl*, N-n-*amyl*, N-1′-*methylbutyl*, and N-*allyl* homologues. It was also readily methylated to pethidine by means of formaldehyde and formic acid.

These compounds and many of those described in Part I (*loc. cit.*) have been submitted to a preliminary pharmacological examination particularly with a view to possible analgesic activity.

Toxicity determinations were made by intravenous injection in mice, using 25 mice for each experiment. The values given in the Table are an assessment of the LD. 50 made from the observed percentage mortalities resulting from doses close in value to the figure stated.

Analgesic activity was estimated by the method described by one of us (R. H. T.) (*Brit. J. Pharmacol.*, 1946, **1**, 113), in which the pain threshold of rats to radiant heat is determined. Tests were carried out on groups of 9 rats, each compound being used three or four times at different dose levels. The pain threshold values were determined ½, 1, 2, and 3 hours after injection in order to get an index at the duration of action, and the maximum increase in pain

threshold has been used in the comparisons. Pethidine and morphine were used as standards of comparison in all the experiments, and the results given in the second column of the Table represent relative analgesic activities (taking morphine as unity) derived from the doses causing approximately a 50% increase in the pain threshold.

The compounds were tested for spasmolytic activity using an isolated preparation of the rabbit small intestine and inducing spasm with carbaminoylcholine and barium chloride. Certain of these substances were also tested on œstrogenic uterine segments from immature female rabbits, caused to contract with adrenaline. The results of these spasmolytic tests are also given in the Table, each figure being the average of six to ten tests upon different muscle segments.

Compound (as hydrochloride).	Toxicity I.V. mice, mg./kg.	Analgesic activity (morphine = 1).	Spasmolytic activity (dilution × 1000). Rabbit ileum. Carbaminoylcholine.	Rabbit ileum. Barium chloride.	Œstrogenic uterus adrenaline.
Pethidine [1, 2]	60	0·1—0·13	500	500	200
4-Phenyl-1-methylpiperidine-4-carboxyamide [2, 3]	—	nil	50	10	—
Norpethidine [1, 2]	65	0·05	150	—	—
N-Ethylnorpethidine [3]	—	0·05	200	—	—
N-*n*-Propylnorpethidine [3]	40	0·15—0·2	200	—	—
N-*iso*Propylnorpethidine	50	0·05	500	—	—
N-*n*-Butylnorpethidine [3]	25	0·15	150	—	—
N-*sec*.-Butylnorpethidine	30	0·12	100	—	—
N-*n*-Amylnorpethidine	12	0·15	—	—	—
N-1′-Methylbutylnorpethidine	—	0·05	—	—	—
N-Allylnorpethidine	50	0·08	150	—	—
N-Benzylnorpethidine [1, 3]	17	0·05	50	—	—
α-Phenyl-α-(β′-aminoethyl)butyrolactone [3]	20	Nil	10	10	Nil
α-Phenyl-α-(β′-methylaminoethyl)-butyrolactone [3]	120	Nil	5	10	10
α-Phenyl-α-(β′-ethylaminoethyl)-butyrolactone [3]	10	Nil	10	10	10
α-Phenyl-α-(β′-diethylaminoethyl)-butyrolactone [3]	—	Nil	—	—	—
α-Phenyl-α-(β′-*n*-propylaminoethyl)-butyrolactone [3]	90	Nil	20	10	10
α-Phenyl-α-(β′-piperidinoethyl)butyrolactone [3]	40	Nil	5,000	2,000	10
α-Phenyl-α-(β′-benzylmethylaminoethyl)butyrolactone [3]	—	Nil	—	—	—
3-Phenyl-3-(β-aminoethyl)-2-pyrrolidone [3]	—	Nil	8	Enhanced contraction	10
3-Phenyl-3-(β-methylaminoethyl)-2-pyrrolidone [3]	20	Nil	10	Enhanced contraction	10
Trasentin	—	—	10,000	2,000	200
Atropine	—	—	100,000	20,000	—

[1] Eisleb, *Ber.*, 1941, **74**, 1446. [2] B.P. 501,135. [3] Part I, *loc. cit.*

It will be seen from the Table that the toxicity of the alkyl homologues of pethidine increases with the length of the alkyl chain and that analgesic activity increases slightly up to the *n*-propyl compound, which is definitely rather more active than pethidine. The butyrolactone compounds show no analgesic action and, with the exception of the piperidine compound, α-phenyl-α-(β′-piperidinoethyl)butyrolactone hydrochloride, are only poorly spasmolytic. The two pyrrolidones are not analgesic and have no very appreciable spasmolytic action.

It can be concluded that lactones and pyrrolidones of these types are unlikely to prove to be substances of therapeutic value and that the *N*-alkyl homologues of pethidine, although some show slightly greater activity as analgesics, are not sufficiently different from, or more potent than, pethidine to prove of greater value.

Experimental.

1-p-*Tosyl*-4-*phenylpiperidine*-4-*carboxylic Acid* (II).—4-Cyano-1-*p*-tosyl-4-phenylpiperidine (Eisleb, *Ber.*, 1941, **74**, 1446) (50 g.), concentrated sulphuric acid (30 ml.), and water (15 ml.) were heated under reflux until the cyanide had dissolved. The solution was then treated with water (20 ml.) and dilution continued at a rate such as to maintain a clear solution. (Total addition of water, about 200 ml.; total

time of reflux, 3 hours.) On cooling, 1-p-*tosyl*-4-*phenylpiperidine*-4-*carboxylic acid* (52 g., 98%) separated. It crystallised from water in rectangular plates, m. p. 228—231° (Found: N, 3·9; S, 8·6. $C_{19}H_{21}O_4NS$ requires N, 3·9; S, 8·9%).

Ethyl 4-*Phenylpiperidine*-4-*carboxylate* (*Norpethidine*) (III).—The acid (II) (10 g.), ethyl alcohol (30 ml.), and sulphuric acid (6 ml.) were refluxed for 3 hours. The solution was poured into water (100 ml.), made strongly alkaline, and extracted with ether. The ethereal solution, on treatment with carbon dioxide, gave *norpethidine carbonate* as a voluminous white solid, which tended to decompose on attempted crystallisation from water, alcohol, and other solvents (Found: C, 68·0; H, 7·6; N, 5·7. $C_{14}H_{19}O_2N,\frac{1}{2}H_2CO_3$ requires C, 65·9; H, 7·6; N, 5·3%). Norpethidine hydrochloride, from the carbonate, crystallised from alcohol–ether in hexagonal tablets, m. p. 134—135° (Found: N, 5·6; Cl, 12·8. Calc. for $C_{14}H_{19}O_2N,HCl$: N, 5·2; Cl, 13·2%).

Ethyl 4-*Phenyl*-1-*methylpiperidine*-4-*carboxylate* (*Pethidine*).—(*a*) Norpethidine carbonate (7 g.), 40% aqueous sodium hydroxide (4·5 ml.), and sufficient alcohol to produce a homogeneous solution were treated slowly with methyl iodide (4·3 g.) with shaking, the mixture being subsequently refluxed for 10 minutes. The alcohol was removed, the residue made strongly alkaline, and the ethereal extract treated with hydrochloric acid. By recrystallisation from alcohol–ether the aqueous residue gave pethidine hydrochloride (2·5 g.), m. p. 185°, identical with a genuine specimen.

(*b*) Norpethidine carbonate (5 g.), 36% formaldehyde solution (4·3 ml.), and 98% formic acid (1·7 g.) were warmed at 100° for ½ hour. The mixture was extracted with ether and the ethereal extract treated with carbon dioxide to remove any norpethidine as carbonate. Evaporation of the filtrate and treatment with hydrochloric acid in the usual way gave pethidine hydrochloride in good yield (3·5 g.).

Ethyl 4-*Phenyl*-1-*ethylpiperidine*-4-*carboxylate*.—Norpethidine (7 g.), 40% sodium hydroxide solution (6 ml.), and sufficient alcohol to give a homogeneous solution were treated with ethyl sulphate and the product worked up in the manner described above for pethidine (*a*). The resulting hydrochloride (3·1 g.), m. p. 196°, was identical with a specimen prepared from ethyl αα-bis-(β′-bromoethyl)phenylacetate (Part I, 1945, 317).

Ethyl 4-phenyl-1-*n*-propylpiperidine-4-carboxylate was prepared from norpethidine carbonate (5 g.), 40% sodium hydroxide solution (3·75 ml.), *n*-propyl iodide (3·65 g.), and a little alcohol by refluxing for ½ hour. The hydrochloride, m. p. 196° from alcohol–ether, was identical with an authentic specimen (Part I, *loc. cit.*).

Ethyl 4-*phenyl*-1-iso*propylpiperidine*-4-*carboxylate*. This was prepared in the same way. The crude alkylation product (base) in ether was treated with carbon dioxide to remove unchanged norpethidine as carbonate. The filtrate gave a good yield of the *hydrochloride*, which crystallised from alcohol–ether in leaflets, m. p. 165—166° (Found: C, 64·9; H, 8·2; N, 4·8; Cl, 11·3. $C_{17}H_{25}O_2N,HCl$ requires C, 65·5; H, 8·3; N, 4·5; Cl, 11·4%). Ethyl 4-phenyl-1-*n*-butylpiperidine-4-carboxylate, prepared in the same way, gave a hydrochloride, m. p. 181—183° (cf. Part I, *loc. cit.*).

Ethyl 4-*phenyl*-1-sec.-*butylpiperidine*-4-*carboxylate*. This was made by heating norpethidine carbonate (1 g.), 33% sodium hydroxide solution (1 ml.), and *sec.*-butyl iodide (1·6 g.) in a sealed tube for 1 hour at 100°. No norpethidine was recovered as carbonate. The *hydrochloride* crystallised from alcohol–ether in plates, (0·3 g.), m. p. 179—180° (depression with the *N*-butyl derivative) (Found: C 66·6; H, 8·8; N, 4·8; Cl, 10·9. $C_{18}H_{27}O_2N,HCl$ requires C, 66·4; H, 8·3; N, 4·3; Cl, 10·9%).

Ethyl 4-*phenyl*-1-n-*amylpiperidine*-4-*carboxylate*. This was made by refluxing norpethidine carbonate (1 g.), 33% sodium hydroxide solution (1 ml.), *n*-amyl iodide (1·7 g.), and a little *n*-amyl alcohol for 1 hour. No norpethidine was recovered. The *hydrochloride* separated from alcohol–ether in hexagonal plates (0·8 g.), m. p. 178—179° (Found: C, 67·0; H, 8·9; Cl, 10·6. $C_{19}H_{29}O_2N,HCl$ requires C, 67·2; H, 8·5; Cl, 10·5%).

Ethyl 4-*phenyl*-1-(1′-*methylbutyl*)*piperidine*-4-*carboxylate*. This was made by alkylating norpethidine carbonate with 2-bromopentane in a sealed tube at 100°. Its *hydrochloride* crystallised from alcohol–ether in rectangular prisms, m. p. 175—176° (depression with the *n*-amyl derivative) (Found: N, 4·4; Cl, 10·6. $C_{19}H_{29}O_2N,HCl$ requires N, 4·1; Cl, 10·5%).

Ethyl 4-*phenyl*-1-*allylpiperidine*-4-*carboxylate*. This was made by refluxing norpethidine carbonate (3 g.), 33% sodium hydroxide solution (2·25 ml.), allyl bromide (3 g.), and a little alcohol, for 10 minutes. The *hydrochloride* (0·8 g.) formed plates, m. p. 162—163°, from alcohol–ether (Found: C, 66·0; H, 7·8; N, 4·6; Cl, 11·5. $C_{17}H_{23}O_2N,HCl$ requires C, 65·9; H, 7·8; N, 4·5; Cl, 11·5%).

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