say for a glyconic acid lactone.[12] The best physical constants previously reported are: L-threonolactone, m.p. 74–76°,[8] $[\alpha]_D^{20}$ + 47.0° (methanol)[3]; phenylhydrazide, m.p. 161–161.5°, $[\alpha]_D^{21}$ + 48.6° (methanol)[3]; brucine salt, m.p. 209–210° dec., $[\alpha]_D^{22}$ −19.3° (H_2O).[3] Despite the high melting point given by Hardegger, *et al.*,[7] these authors report $[\alpha]_D$ −27.0° (H_2O) for the brucine salt, indicating the presence of optically active impurities; this suggests that the lower melting (65–68°) material obtained by Gätzi and Reichstein[3] was purer.

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Strong Analgesics. Some Ethyl 1-Alkyl-4-phenylpiperidine-4-carboxylates

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Some time ago, it was shown,[2] that when the *N*-methyl substituent of meperidine, ethyl 1-methyl-4-phenylpiperidine-4-carboxylate hydrochloride, was replaced by lower alkyl groups the analgesic potency remained relatively constant although the toxicity gradually increased.

Recently it was reported[3] that replacement of the *N*-methyl substituent of meperidine by aralkyl groups other than benzyl gave compounds having significantly higher analgesic potency. It seemed of interest to us to see if relatively long alkyl groups would effect the same enhancement of analgesic potency.

Accordingly, analogs were prepared wherein the *N*-methyl substituent was replaced by various relatively long chain alkyl groups, both straight and branched.

The alkylation of ethyl 4-phenylpiperidine-4-carboxylate was accomplished using either alkyl halides or toluenesulfonates.

The pharmacological evaluation of these compounds for analgesic potency by the Bass, Vander Brook modification[4] of the D'Amour, Smith rat thermal stimulus method[5] will be reported more fully elsewhere, but a brief summary can be given here. It is apparent that the substituent on the nitrogen of meperidine can be extended to at least nine carbons without loss of any analgesic potency; in fact, the compounds having straight chains and one of the branched chain compounds are more potent than meperidine itself.

EXPERIMENTAL

Ethyl 1-heptyl-4-phenylpiperidine-4-carboxylate hydrochloride. A mixture of ethyl 4-phenylpiperidine-4-carboxylate hydrochloride (13.5 g., 0.05 mole), *n*-heptyl bromide (8.95 g., 0.05 mole), sodium carbonate (20 g.), and *n*-butyl alcohol (100 ml.) was refluxed with stirring for 24 hr. The solids were removed by filtration and a small piece of Dry Ice added to the filtrate to precipitate any secondary amine still present. The filtrate was then concentrated *in vacuo* on a steam bath and the residual oil taken up in ether. A small amount of precipitate was removed by filtration and ethereal hydrogen chloride was added to the filtrate. The product was collected and crystallized from ethyl acetate (150 ml.), then recrystallized from a mixture of benzene (65 ml.) and cyclohexane (65 ml.). There was obtained 14.3 g. (78.0%) of product, m.p. 146.4–149°.

2-Hexyl-p-toluenesulfonate. 2-Hexanol (255 g., 2.5 moles) and pyridine (595 g., 7.5 moles) were stirred in an open beaker and cooled to 0°. *p*-Toluenesulfonyl chloride (858 g., 4.5 moles) was added portionwise over 3 hr. at such a rate as to keep the temperature at about 15°. When the addition was completed, the reaction mixture was allowed to reach room temperature. The unchanged *p*-toluenesulfonyl chloride was hydrolyzed by addition of 150 ml. of water and 200 ml. of pyridine. After hydrolysis was completed, concd. hydrochloric acid was added, the aqueous layer was separated, and the organic layer was washed with water, dilute sodium bicarbonate solution, and water again. Traces of water were removed from the organic layer by heating at 50–60° at reduced pressure, first with a water pump and then with a mechanical pump. There was obtained 533 g. (82%) of yellow oil which was used without further purification.

Ethyl 1-(2-hexyl)-4-phenylpiperidine-4-carboxylate. Methane sulfonate. Ethyl 4-phenylpiperidine-4-carboxylate hydrochloride (1700 g., 6.3 moles) was dissolved in 2.5 l. of water. The solution was made basic with 35% aqueous sodium hydroxide, extracted with ether, the extract dried over anhydrous sodium sulfate, and concentrated to an oil. 2-Hexyl-*p*-toluenesulfonate (768 g., 3.0 moles) was added all at once. The reaction mixture turned into a thick magma after stirring for 3 hr. at room temperature. Heating on the steam bath caused the mixture to liquify, then resolidify after 1 hr. Heating was continued for 1 hr. more and the mixture allowed to stand overnight. Three liters of water was added to the solid reaction mixture, which was heated on the steam bath until solution was complete. The cooled solution was extracted with ether several times. A 750-ml. portion of water was added to the ether extracts and 252 ml. of concd. hydrochloric acid added with cooling. In 15 min. the product precipitated. After drying there was obtained 848 g. (80%) of ethyl 1-(2-hexyl)-4-phenylpiperidine-4-carboxylate hydrochloride, m.p. 162–164. A 1098-g. sample (3.1 moles) of the above hydrochloride was dissolved in 3 l. of water, made basic with 35% sodium hydroxide, and extracted with benzene. The extract was concentrated *in vacuo* and the oily residue dissolved in 250 ml. of isopropyl alcohol and 4 l. of ether. Methanesulfonic acid (328 g., 3.41 moles) was added with cooling and stirring. The product

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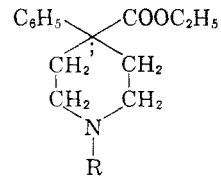
TABLE I

ETHYL 1-ALKYL-4-PHENYLPIPERIDINE-4-CARBOXYLATES



R—	Formula	Yield, %	M.P.	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Chlorine, % Calcd.	Chlorine, % Found	Activity[d]
$CH_3(CH_2)_5$—	$C_{20}H_{32}ClNO_2 \cdot HCl$	48.6	160.0–161.4	67.87	67.81	9.12	9.10	10.02	10.02	6.7
$CH_3(CH_2)_6$—	$C_{21}H_{34}ClNO_2 \cdot HCl$	78.0	146.4–149.0	68.54	68.40	9.31	9.26	9.64	9.49	3.3
$CH_3(CH_2)_7$—	$C_{22}H_{36}ClNO_2 \cdot HCl$	68.4	137.0–138.0	69.16	69.44	9.50	9.09	9.28	8.99	4.0
$CH_3(CH_2)_8$—	$C_{23}H_{38}ClNO_2 \cdot HCl$	43.0	132.4–134.2	69.76	69.58	9.67	9.47	8.95	8.77	2.5
$CH_3(CH_2)_9$—	$C_{24}H_{40}ClNO_2 \cdot HCl$	28.7	135.4–136.2	70.30	70.61	9.83	10.48	8.65	8.60	0
$CH_3(CH_2)_{11}$—	$C_{26}H_{44}ClNO_2 \cdot HCl$	16.4	131.6–132.6	71.27	71.35	10.13	10.01	8.09	8.16	0
CH_3 \ $CHCH_2CH_2$— / C_2H_5	$C_{20}H_{32}ClNO_2 \cdot HCl$	59.9	163.4–165.4	67.87	67.97	9.12	9.59	10.02	9.99	3.0
CH_3 \ CH— / C_4H_9	$C_{20}H_{31}NO_2$[c]	68.8	120–122	60.97	61.01	8.53	8.56	7.75[a]	7.78	5.8
C_2H_5 \ CH— / C_4H_9	$C_{21}H_{34}ClNO_2 \cdot HCl$	17.6	145.0–147.4	8.69[b]		8.70		9.63	9.54	1.7
C_2H_5 \ CH— / C_3H_7	$C_{20}H_{32}ClNO_2 \cdot HCl$	35.6	179.6–182.6	9.04[b]		8.95		10.02	9.99	0.23
Meperidine										1

[a] Analyzed for sulfur. [b] Analyzed for oxygen. [c] B. CH_3SO_3H salt. [d] Relative to meperidine.

precipitated after a few minutes of stirring. The product was collected, washed with ether and dried; yield 1089 g. (86%), m.p. 120–122°.

Anal. Calcd. for $C_{20}H_{31}NO_2 \cdot CH_3SO_3H$: C, 60.97; H, 8.53; S, 7.75. Found: C, 61.01; H, 8.56; S, 7.78.

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N-Substituted *N'*-Phenylureas

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A factor which stimulated growth in mature carrot phloem cells has been identified as 1,3-diphenylurea.[1] The possibility that other phenylurea derivatives might possess physiological activity is suggested by the fact that various structural modifications of another plant growth factor, Kinetin[2] [6-(2-furfurylamino)purine], have been found to be effective in stimulating biological responses in a number of assay systems. For example, the furfuryl group of Kinetin can be replaced, with retention of biological activity, by phenyl-,[3] ω-phenylalkyl-,[4] ω-cyclohexylalkyl-,[5] and heterocyclicaminopurines.[6] Accordingly, a number of substituted amines were condensed with phenylisocyanate to produce the corresponding *N*-substituted *N'*-phenylureas. These compounds were subsequently examined in several biological assay systems.

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