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ESTERS OF N-SUBSTITUTED PIPERIDINE CARBOXYLIC ACIDS[1]

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As part of an extended search for improved local anesthetics, two series of β-diethylaminoethyl esters of N-substituted piperidine carboxylic acids (IV, VII) have been synthesized. The N-substituent groups were phenyl, benzyl, phenethyl, and *n*-butyl.

The reaction of a dihalogenated ester (II or V) with three molar proportions of the appropriate primary amine gave a piperidine derivative (III or VI). The ethyl esters resulting from the ring closure were converted by base-catalyzed alcoholysis to the corresponding β-diethylaminoethyl esters (IV, VII). Hydrochloride salts of all the piperidines were prepared, but in several cases, notably those prepared from the esters of dicarboxylic acids, the products were too highly hygroscopic for analysis. McElvain (1) also reported difficulties in crystallizing hydrochlorides of certain piperidine esters, though he did not mention hygroscopic properties.

The properties of the new compounds are listed in Table I. The results of pharmacological testing will be reported elsewhere.

In the series of esters of piperidine-2,6-dicarboxylic acids (VI, VII), questions of stereoisomerism arise. If the diethyl α,ε-dibromopimelate (V) which was used in the closure reaction with amines is the meso isomer, the resulting piperidine ethyl esters (VI) should have the meso *cis* configuration. If the dibromo ester is the racemic mixture, the products should be the racemic *trans* piperidine esters. No work on the stereoisomerism of α,ε-dibromopimelic acid or its esters had been published at the time of this investigation. We prepared the diethyl ester (V), following the procedure of Willstätter (2), by typical α-bromination of pimelic acid and direct treatment of the bromination mixture with ethanol. All of the product having the correct bromine content distilled at 150–153° (2 mm.). Similarly, there was no evidence of stereoisomerism in any of the piperidines prepared from this dibromopimelic ester. Fischer (3) and Schmidt (4) reported isomeric piperidine-2,6-dicarboxylic acids obtained from the reaction of ammonia and methylamine, respectively, with the diethyl α,ε-dibromopimelate prepared by Willstätter's procedure (2). However, in each synthesis the yields of both isomers were low, and their *cis-trans* configurations were not determined. Recently, the stereoisomerism of α,ε-dibromopimelic acid has been partially elucidated. Wilson (5) and Fehnel and Oppenlander (6) have succeeded in isolating the meso isomer, which apparently predominates over the racemic mixture when pimelyl chloride is brominated and the product is decomposed with water or formic acid.

Even had we established the configurations of our ethyl esters of piperidine-

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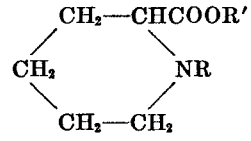
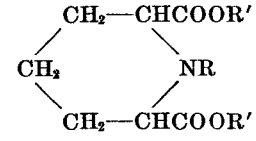
TABLE I

PIPERIDINE ESTERS



(Type A)

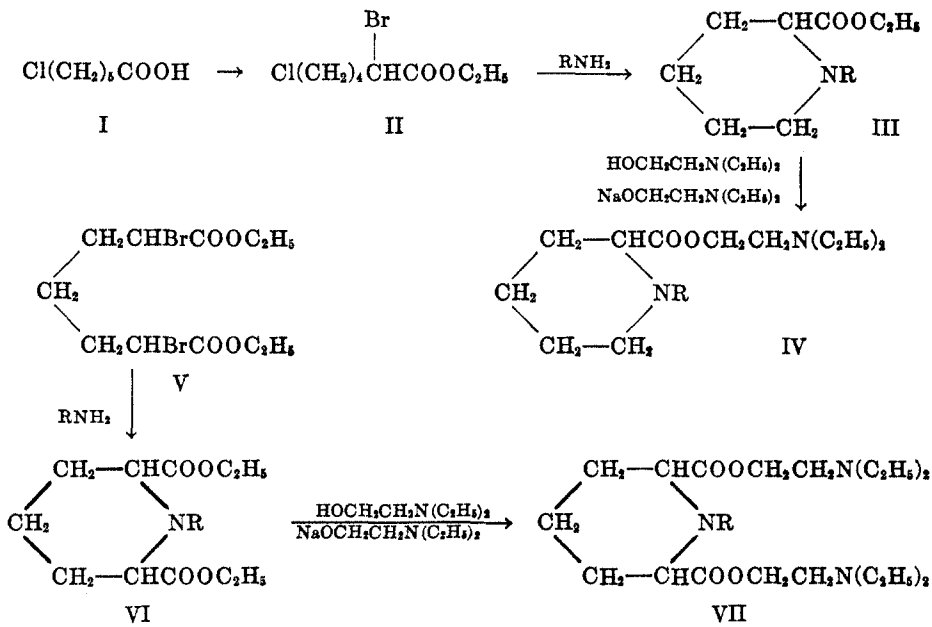


(Type B)

Type	R	R′	Yield, %	B.p. °C.	B.p. mm.	M.p.,[a] °C.	n_D^{20}	Formula	Analysis N Calc'd	Analysis N Found	Analysis Cl Calc'd	Analysis Cl Found
A	$-C_6H_5$	$-C_2H_5$	40	106–108	0.05		1.5391	$C_{14}H_{19}NO_2$	6.00	6.19		
	hydrochloride					137–137.5		$C_{14}H_{19}ClNO_2$	5.19	5.14	13.15	13.26
A	$-C_6H_5$	$-C_2H_4N(C_2H_5)_2$	66	145–150	0.5		1.5250[b]	$C_{18}H_{28}N_2O_2$	9.20	8.92		
	monohydrochloride					131–132		$C_{18}H_{29}ClN_2O_2$	8.22	8.25	10.40	10.32
A	$-CH_2C_6H_5$	$-C_2H_5$	66	125–126	2		1.5135	$C_{15}H_{21}NO_2$	5.66	5.70		
	hydrochloride					150–151		$C_{15}H_{22}ClNO_2$	4.93	5.24	12.49	12.07
A	$-CH_2C_6H_5$	$-C_2H_4N(C_2H_5)_2$	25	165–170	2		1.5082	$C_{19}H_{30}N_2O_2$	8.80	9.10		
	dihydrochloride					196–196.5		$C_{19}H_{32}Cl_2N_2O_2$	7.16	7.41	18.12	17.97
A	$-CH_2CH_2C_6H_5$	$-C_2H_5$	70	114–115	.2		1.5100[b]	$C_{16}H_{23}NO_2$	5.36	5.19		
	hydrochloride					139.5–140		$C_{16}H_{27}ClNO_2$	4.70	4.63	11.91	11.87
A	$-CH_2CH_2C_6H_5$	$-C_2H_4N(C_2H_5)_2$	63	145–146	.15		1.5058[b]	$C_{20}H_{32}N_2O_2$	8.43	8.80		
A	$-(CH_2)_3CH_3$	$-C_2H_5$	68	122–124	12		1.4520	$C_{12}H_{23}NO_2$	6.57	6.32		
	hydrochloride					122–122.5		$C_{12}H_{24}ClNO_2$	5.61	5.38	14.20	13.70
A	$-(CH_2)_3CH_3$	$-C_2H_4N(C_2H_5)_2$	57	110–111	.25		1.4626					
	dihydrochloride					146–148		$C_{16}H_{34}Cl_2N_2O_2$	7.84	7.65	19.84	19.77
B	$-C_6H_5$	$-C_2H_5$	71	140–143	.5		1.5192[b]	$C_{17}H_{23}NO_4$	4.59	4.43		
	hydrochloride					128–130		$C_{17}H_{24}ClNO_4$	4.10	3.93	10.37	10.39
B	$-C_6H_5$	$-C_2H_4N(C_2H_5)_2$	36	188–190	.07		1.5075[b]	$C_{25}H_{41}N_3O_4$	9.39	9.88		
B	$-CH_2C_6H_5$	$-C_2H_5$	55	135–140	.2		1.5045	$C_{18}H_{25}NO_4$	4.39	4.55		
B	$-CH_2C_6H_5$	$-C_2H_4N(C_2H_5)_2$	61	195–197	.2		1.4996[b]	$C_{26}H_{43}N_3O_4$	9.10	8.92		
B	$-(CH_2)_3CH_3$	$-C_2H_5$	69	126–129	2		1.4582	$C_{15}H_{27}NO_4$	4.91	4.84		
B	$-(CH_2)_3CH_3$	$-C_2H_4N(C_2H_5)_2$	61	190–200	2		1.4703	$C_{23}H_{45}N_3O_4$	9.83	9.38		

[a] All melting points are corrected. [b] n_D^{25}.

dicarboxylic acids (VI), we would be none the wiser concerning the configurations of the β-diethylaminoethyl esters, since the strongly basic conditions necessary for the alcoholysis are known to effect rapid racemization of esters with hydrogen on an asymmetric α-carbon atom (7). Therefore, since the principal aim of our work was the preparation of the β-diethylaminoethyl esters for preliminary pharmacological screening, we devoted no further effort to the question of stereoisomerism.



EXPERIMENTAL

6-Chlorohexanoic acid (I). A solution of 36.8 g. (0.71 mole) of sodium cyanide (assaying 95% NaCN) in 60 ml. of water was added dropwise to a solution of 141 g. (1.0 mole) of 1,5-dichloropentane in 200 ml. of 95% ethanol in a 1-liter three-neck flask equipped with dropping-funnel, reflux condenser, and mechanical stirrer. Stirring and refluxing were maintained during the three-hour addition period and 18 hours thereafter. The reaction mixture was diluted with 300 ml. of water and extracted with three portions of chloroform. The chloroform was removed by distillation, and the residual oil was distilled under diminished pressure. The fraction collected at 75–105° (14 mm.) weighed 82 g. and consisted of unreacted 1,5-dichloropentane and entrained ethanol and chloroform. The fraction collected at 105–130° (9 mm.), containing the 6-chlorohexanonitrile (with some dichloropentane and pimelonitrile), was refluxed with concentrated hydrochloric acid for 16 hours. The mixture was cooled and extracted with three portions of chloroform. The combined extracts were dried over calcium sulfate. The dried extract was then concentrated by distillation of the chloroform, and the residual oil was distilled under diminished pressure. The clear colorless oil collected at 136–138° (8.5 mm.) weighed 21.7 g. and froze to pure white crystals when chilled in an ice-bath. Yield 20%, based on sodium cyanide. The acid was purified by redistillation. M.p. 24–26°. B.p. 136–137° (8.5 mm.)

Anal. Calc'd for $C_6H_{11}ClO_2$: C, 47.85; H, 7.36; Cl, 23.54.
Found: C, 47.60; H, 7.60; Cl, 23.37.

dl-Ethyl 2-bromo-6-chlorohexanoate (II). A mixture of 34.8 g. (0.231 mole) of 6-chlorohexanoic acid and 2 ml. of phosphorus tribromide was placed in the usual apparatus and 46.5 g. (0.29 mole, 16 ml.) of dry bromine was added dropwise over the course of two hours, during stirring and warming over a 100-watt lamp. The heating was continued for an additional 18 hours. The brown reaction mixture was then dissolved in 300 ml. of absolute ethanol, and the solution was refluxed for ten hours. The excess alcohol was removed by distillation, and the residue was mixed with water and extracted with three portions of ether. The combined extracts were washed with sodium carbonate solution and dried over calcium sulfate. The ether was then removed by distillation, and the residual oil was distilled under diminished pressure. The clear, colorless oil collected at 128–132° (7 mm.) weighed 42.6 g. Yield 72%. B.p. 130–131° (7 mm.), n_D^{20} 1.4783.

Anal. Calc'd for $C_8H_{14}BrClO_2$: Total halogen if reported as Br, 54.72. Found: Total halogen as Br, 54.96.

Piperidine esters by closure reaction of dihalogenated esters with primary amines. One-tenth mole of dihaloester (ethyl 2-bromo-6-chlorohexanoate (II) or diethyl α,ϵ-dibromopimelate (V)) was mixed with 0.30 mole of the appropriate freshly-distilled primary amine (aniline, benzylamine, 2-phenylethylamine, or *n*-butylamine), 60–100 ml. of dry benzene, and 0.5 g. of powdered potassium iodide. After any slight evolution of heat had ceased, the mixture was allowed to stand at room temperature for one to three hours, then refluxed for 48 to 72 hours, during which amine salts slowly crystallized. The mixture was added to water and extracted with ether. The ether extract was then shaken with three small portions of 6 *N* sulfuric acid, the combined aqueous extracts were made slightly alkaline with sodium hydroxide, and the resulting free base was extracted with ether. After drying over calcium sulfate, the extract was concentrated by distillation of the ether, and the residual oil was distilled under a vacuum. Redistillation of the major fraction yielded clear and colorless or very pale yellow oil.

β-Diethylaminoethyl esters of piperidine carboxylic acids. β-Diethylaminoethyl alcohol in ten-fold excess was placed in a 100-ml. distilling flask with a fractionating (Vigreux) neck. Clean sodium metal (about 0.02 gram-atom per mole of amino alcohol) was dissolved in the amino alcohol, and then the appropriate ethyl ester of a piperidine carboxylic acid (III or VI, 0.02 to 0.05 mole) was added. The mixture was heated in an oil-bath at a temperature (about 170°) sufficient to cause the amino alcohol solvent to reflux gently but not to distill from the top of the fractionating column. Ethanol slowly distilled as it was displaced by alcoholysis. The heating period varied between 18 and 36 hours. The excess β-diethylaminoethyl alcohol was then removed by distillation at reduced pressure, and the oily semisolid residue was taken up in ether and washed with water. The ether solution was dried over calcium sulfate and then concentrated by distillation of the ether. The residual oil was distilled under vacuum. Redistillation of the major fraction yielded clear yellow oil.

Hydrochloride salts of the piperidine esters were precipitated from solutions of the bases in dry ether by the dropwise addition of a solution of hydrogen chloride in dry ether, during vigorous stirring. The usually hygroscopic precipitates were collected on a filter and immediately placed in a vacuum desiccator charged with sodium hydroxide pellets, where they remained for several days. The salts were then recrystallized from dry dioxane or dioxane-ethanol mixtures. In some cases, repeated attempts with varying proportions of base and hydrogen chloride always yielded salts that were too highly hygroscopic to handle, often absorbing water even while in the vacuum desiccator.

1-Phenylpiperidine-2,6-dicarboxylic acid. A mixture of 6.1 g. (0.020 mole) of diethyl 1-phenylpiperidine-2,6-dicarboxylate, 8.2 g. (0.2 mole) of sodium hydroxide, 130 ml. of 95% ethanol, and 50 ml. of water was refluxed for one hour, during which a small amount of fine white precipitate formed. This was separated by filtration, and the filtrate was further refluxed for 14 hours. Meanwhile the white precipitate was dissolved in water, and the solution was acidified with dilute hydrochloric acid, whereupon fine colorless needles separated. From the long-refluxed solution, similar crystals formed after removal of the

ethanol and acidification of the residue. Both samples had the same m.p. 126–128° (with decomposition). This was found to be a monohydrate. Yield, 2.18 g. (41%). Neutralization equivalent, Calc'd for $C_{11}H_{13}N(COOH)_2 \cdot H_2O$: 133.5; Found (phenolphthalein indicator): 134.0. Upon prolonged heating at 100° at 15 mm. pressure, a sample lost one molar equivalent of water and melted at 180–190° with decarboxylation. It also decomposed slowly when kept at 170°.

Anal. Calc'd for $C_{13}H_{15}NO_4$: N, 5.62. Found: N, 5.65.

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