

Alkyl- and Dialkylamides of *p*-Aminobenzoic Acid

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In continuation of a study of new types of local anesthetics,<sup>1</sup> the normal C<sub>1</sub> to C<sub>5</sub> alkyl- and dialkylamides and the piperidide of *p*-aminobenzoic acid are described in this paper. In contrast to the large amount of recorded research on esters of *p*-aminobenzoic acid, the literature contains no reference to this class of compounds. Local anesthetic properties could be expected from them not only because of their analogy to the corresponding strongly active esters, but also in view of the fact that amides of heterocyclic acids have received attention as local anesthetics.<sup>2</sup>

## Experimental

**Alkyl- and Dialkyl-*p*-nitrobenzamides.**—0.05 mole of *p*-nitrobenzoyl chloride was allowed to react at 50–60° with 0.055 mole of amine or dialkylamine in water containing 0.075 equivalent of sodium carbonate. Mechanical agitation was employed, and with two exceptions the *p*-nitrobenzamides crystallized after a short time. They were recrystallized from dilute ethanol. Most of them are readily soluble in ethanol, sparingly so in water; the dimethylamide is also fairly soluble in water. They were not analyzed; the melting points are given in the table.

**Alkyl- and Dialkyl-*p*-aminobenzamides.**—The nitroamides were reduced in the usual manner with stannous chloride and hydrochloric acid at 50–60°, with addition of glacial acetic acid to increase the solubility. After cooling and overneutralizing with sodium hydroxide, some of the *p*-aminobenzamides separated in crystalline form and their further purification offered no difficulty; others remained oily and were isolated in form of their hydrochlorides under anhydrous conditions. Melting points and analytical data, as given in the table, therefore refer in some instances to the free base, in others to the hydrochloride. The diamylamide and its hydrochloride did not

(1) Wenker, *THIS JOURNAL*, **60**, 156 (1938).

(2) German Patents 537,140, 540,697, 540,698.

TABLE I

*n*-ALKYL- AND *n*-DIALKYL-*p*-NITRO- AND *p*-AMINO BENZAMIDES

Alkyl-( )- dialkyl- <i>p</i> -nitro ( <i>p</i> -amino) benzamide	<i>p</i> -Nitro m. p., °C.	Formula	<i>p</i> -Amino	
			M. p., °C.	Analyses, % Calcd. Found
Methyl	217	C <sub>8</sub> H <sub>10</sub> N <sub>2</sub> O	180 <sup>a</sup>	N 18.7 18.5
Ethyl	151	C <sub>9</sub> H <sub>12</sub> N <sub>2</sub> O·HCl	227 <sup>b</sup>	Cl 17.7 17.5
<i>n</i> -Propyl	103	C <sub>10</sub> H <sub>14</sub> N <sub>2</sub> O·HCl	223 <sup>b</sup>	Cl 16.6 16.5
<i>n</i> -Butyl	104 <sup>c</sup>	C <sub>11</sub> H <sub>16</sub> N <sub>2</sub> O	99 <sup>d</sup>	N 14.6 14.7
<i>n</i> -Amyl	92	C <sub>12</sub> H <sub>18</sub> N <sub>2</sub> O	98 <sup>d</sup>	N 13.6 13.6
Dimethyl	97	C <sub>8</sub> H <sub>12</sub> N <sub>2</sub> O	153 <sup>e</sup>	N 17.1 17.1
Diethyl	65	C <sub>11</sub> H <sub>16</sub> N <sub>2</sub> O	125 <sup>e</sup>	N 14.6 14.8
Di- <i>n</i> -propyl	41	C <sub>14</sub> H <sub>20</sub> N <sub>2</sub> O·HCl	154 <sup>e</sup>	Cl 13.8 14.0
Di- <i>n</i> -butyl	..	C <sub>15</sub> H <sub>22</sub> N <sub>2</sub> O·HCl	141 <sup>e</sup>	Cl 12.5 12.3
Di- <i>n</i> -amyl	..	C <sub>17</sub> H <sub>26</sub> N <sub>2</sub> O·HCl	..	Cl 11.4 11.5
Piperidyl	121	C <sub>11</sub> H <sub>16</sub> N <sub>2</sub> O	162 <sup>e</sup>	N 13.7 13.7

<sup>a</sup> Crystallized from water. <sup>b</sup> Crystallized from ethanol-  
amyl acetate. <sup>c</sup> Coleman and Howells, *THIS JOURNAL*, **45**,  
3084 (1923), report a melting point of 102.5–103°. <sup>d</sup> Crystallized from dilute methanol. <sup>e</sup> Crystallized from amyl acetate.

crystallize; the latter was analyzed after drying *in vacuo* over calcium oxide. The free *p*-aminobenzamides are fairly soluble in water; the hydrochlorides dissolve easily with acid reaction.

**Local Anesthetic Properties of the *p*-Aminobenzamides.**  
—The mono- and diamides of the methyl and ethyl series and the piperidide are without effect on the tongue. The monopropyl compound is slightly effective; the mono-butyl- and amylamide as well as the three higher dialkylamides are strong surface anesthetics.

## Summary

The normal C<sub>1</sub> to C<sub>5</sub> alkyl and dialkyl amides and the piperidide of *p*-aminobenzoic acid, as well as the intermediate *p*-nitrobenzamides, have been described. The higher members of the series are local anesthetics.

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