

**522. Bisquaternary Ammonium Salts. Part III.\* 4-Alkylbenzene-1 :  $\omega$ -bistrialkylammonium Salts.**

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A series of 4-alkylbenzene-1 :  $\omega$ -bistrialkylammonium di-iodides (I) (where R = R' = R'' = Me or Et and  $n$  is 0—6) has been prepared. Some of these compounds are of interest as ganglion or neuromuscular blocking agents.

THE work described in this paper was undertaken in 1950—1952 in the hope of obtaining compounds of greater pharmacological value than the well-known polymethylene bisquaternary ammonium salts.<sup>1,2</sup> The first two compounds prepared (I; R = R' = R'' = Me;  $n$  = 0 and 1) have no ganglion-blocking activity, but the next member of the series ( $n$  = 2) is very active. Ganglion-blocking activity was retained where  $n$  = 3, but higher homologues ( $n$  = 4—6) were found, as expected, to be predominantly neuromuscular



blocking agents. Members of some related homologous series (I; R = R' = Me, R'' = Et; R = Me; R' = R'' = Et; R = R' = R'' = Et) have also been prepared. Details of the pharmacological work have been published,<sup>3</sup> and some of the compounds are the subject of patent specifications.<sup>4</sup> The synthesis of 4-ethylbenzene-1 : 2'-bis(trimethylammonium iodide) (I; R = R' = R'' = Me;  $n$  = 2) was described by Borovička *et al.*<sup>5</sup> after the completion of the present work.

Hoffmann<sup>6</sup> first described, though inadequately, the preparation of *p*-phenylenebis(trimethylammonium iodide) (I; R = R' = R'' = Me;  $n$  = 0). In the present work, tetra-*N*-methyl-*p*-phenylenediamine,<sup>7</sup> prepared from *p*-phenylenediamine by the Eschweiler-Clarke reaction, readily furnished the monoquaternary salt<sup>8</sup> when treated with methyl iodide. It is not surprising (cf. Fahim and Galaby<sup>9</sup>) that this compound was converted into the bisquaternary derivative only under drastic conditions; when it was treated with methyl iodide in ethylene glycol at 100° (sealed tube) for less than 70 hr., unchanged

\* Part II, *J.*, 1956, 3941.

<sup>1</sup> Barlow and Ing, *Brit. J. Pharmacol.*, 1948, **3**, 298.

<sup>2</sup> Paton and Zaimis, *ibid.*, 1949, **4**, 381.

<sup>3</sup> Wien and Mason, *ibid.*, 1953, **8**, 306.

<sup>4</sup> Leeds and Ashley, B.P. 705,506, 705,528, 748,217; Wien, Ashley, and Leeds, B.P. 748,214.

<sup>5</sup> Borovička, Šedivý, Jilek, and Protiva, *Chem. Listy*, 1955, **49**, 231.

<sup>6</sup> Hofmann, *Compt. rend.*, 1863, **56**, 992.

<sup>7</sup> Meyer, *Ber.*, 1903, **36**, 2979.

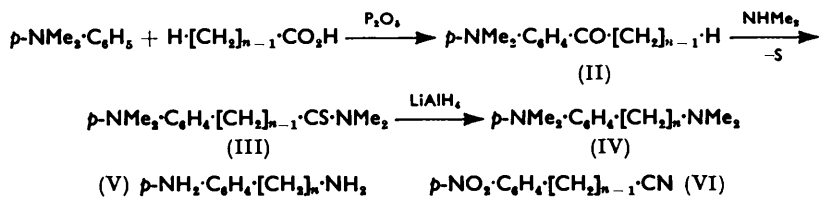
<sup>8</sup> Pinnow and Pistov, *Ber.*, 1894, **27**, 603.

<sup>9</sup> Fahim and Galaby, *J.*, 1950, 3529.

monoquaternary compound remained. 4-Methylbenzene-1 : 1'-bis(trimethylammonium iodide) (I; R = R' = R'' = Me; n = 1) was obtained without difficulty on treating *p*-dimethylaminobenzylamine<sup>10</sup> with methyl iodide and sodium carbonate in boiling methanol.

No difficulty was experienced in the preparation of the important ganglionic blocking agent 4-ethylbenzene-1 : 2'-bis(trimethylammonium iodide) (I; R = R' = R'' = Me; n = 2) from *p*-dimethylaminophenethylamine, methyl iodide, and sodium carbonate in boiling methanol. Braun and Blessing<sup>11</sup> claimed to have prepared this compound from both *p*-amino- and *p*-dimethylamino-phenethylamine. No details were given but it was stated that experiments with *p*-aminophenethylamine gave erratic results (cf. Borovička *et al.*<sup>5</sup>). However, we have had no difficulty in preparing the compound in one operation from either starting material. The product obtained by Braun and Blessing<sup>11</sup> from *p*-dimethylaminophenethylamine is described as having m. p. >300°. Our product had m. p. 255°, and this agrees with that recorded (259—260°) by Borovička *et al.*<sup>5</sup> who also comment on the high m. p. given by the German workers. In the present work *p*-aminophenethylamine was prepared by catalytic reduction of *p*-nitrobenzyl cyanide, and *p*-dimethylaminophenethylamine by Curtius degradation of β-*p*-dimethylaminophenylpropionic acid.<sup>12</sup>

The bisquaternary salts (I; R = R' = R'' = Me; n = 3—5) were prepared from the appropriate 1-dimethylamino-ω-*p*-dimethylaminophenylalkanes. These were prepared by the general method (II—IV). The *n*-alkyl *p*-dimethylaminophenyl ketones (II; n = 2 and 3) were first synthesised in this way by Nineham<sup>13</sup> whose procedure was used for the homologues (II; n = 4 and 5). This work is included in the above publication,<sup>13</sup> together with proofs of the structure of the compounds (II; n = 3 and 4). The structure of the



ketone (II; n = 5) was established by hydrolysing the derived *NN*-dimethyl-δ-*p*-dimethylaminophenylthiovaleramide (III; n = 5) to the corresponding valeric acid, identical with that synthesised by standard methods from δ-*p*-nitrophenylvaleric acid.<sup>14</sup> The Kindler-Willgerodt reaction was used to convert the aldehyde (II; n = 1) and the ketones (II; n = 2—5) into the thioamides (III; n = 1—5). Malodorous, coloured, oily by-products were formed in increasing amounts on ascending the series, so that yields rapidly diminished (see Table 1): the thioamides are however crystalline, and were isolated without undue difficulty even when the yield was as low as 5%. The thioamides (III; n = 1—5) were smoothly and efficiently converted into the diamines (IV; n = 1—5).

The bisquaternary salts (I; R = R' = R'' = Me; n = 3—5) were prepared without difficulty from the amines (IV). The salt (I; R = R' = R'' = Me; n = 6) was prepared by treating 6-*p*-aminophenylhexylamine with methyl iodide and sodium carbonate; the two homologues (I; R = R' = R'' = Me; n = 2 and 3) were similarly prepared. The 4-alkylbenzene-1 : ω-bis(ethyltrimethylammonium iodides) (I; R = R' = Me, R'' = Et; n = 1—5) were prepared by treating the diamines (IV) with ethyl iodide, reaction being more sluggish than with methyl iodide.

<sup>10</sup> Shoppee, *J.*, 1931, 1237.

<sup>11</sup> Braun and Blessing, *Ber.*, 1923, 56, 2160.

<sup>12</sup> Shoppee, *J.*, 1930, 968.

<sup>13</sup> Nineham, *J.*, 1952, 635.

<sup>14</sup> Plati, Strain, and Warren, *J. Amer. Chem. Soc.*, 1943, 65, 1273.

The 4-alkylbenzene-1:ω-bis(triethylammonium iodides) (I; R = R' = R'' = Et; n = 2—6) were prepared from the bisprimary amines (V), ethyl iodide, and sodium carbonate. The required ω-p-aminophenylalkylamines (V; n = 2—6) were obtained by

TABLE 1. ω-p-Dimethylaminophenyl-n-alkane-1-(NN-dimethylthiocarboxamides) (III).

n - 1	Formula	Yield (%)	Form (solvent)	M. p.	Found (%)			Required (%)		
					C	H	N	C	H	N
0	C <sub>11</sub> H <sub>16</sub> N <sub>2</sub> S	55	Needles (C <sub>6</sub> H <sub>6</sub> -Pet *)	105—106°	63.6	7.9	13.5	63.5	7.7	13.5
1	C <sub>12</sub> H <sub>18</sub> N <sub>2</sub> S	20	Needles (EtOH)	102—103	64.9	8.1	12.5	64.9	8.1	12.6
2	C <sub>13</sub> H <sub>20</sub> N <sub>2</sub> S	14	Plates (EtOH)	102—103	66.4	8.5	11.8	66.1	8.5	11.9
3	C <sub>14</sub> H <sub>22</sub> N <sub>2</sub> S	5—7	Plates (EtOH)	83—84	67.2	9.0	11.1	67.2	8.8	11.2
4	C <sub>15</sub> H <sub>24</sub> N <sub>2</sub> S	3—5	Plates (EtOH)	79	68.1	9.2	10.8	68.2	9.1	10.6

\* Pet = light petroleum (b. p. 60—80°).

catalytic hydrogenation of the ω-p-nitrophenyl-n-alkyl cyanides (VI). The cyanides (VI; n = 2 and 3) were prepared by nitrating benzyl and 2-phenethyl cyanide, respectively; the latter nitration is described by Zemplen *et al.*,<sup>15</sup> the structure of their product now being proved by hydrolysis to the known acid.<sup>16</sup> The other homologous cyanides (VI; n = 4—6) were prepared from ω-p-nitrophenyl-butyric,<sup>17</sup> -valeric,<sup>14</sup> and -hexanoic acids.<sup>17</sup> With phosphorus pentachloride and then ammonia these acids yielded the amides which were converted into the cyanides by dehydration with thionyl chloride. In the preparation

TABLE 2. 1-Dimethylamino-ω-p-dimethylaminophenylalkanes (IV).

n	Formula	Yield (%)	B. p./mm.*	Found (%)			Required (%)		
				C	H	N	C	H	N
1	C <sub>11</sub> H <sub>18</sub> N <sub>2</sub>	68	135°/15	73.8	10.1	15.5	74.2	10.1	15.7
2	C <sub>12</sub> H <sub>20</sub> N <sub>2</sub>	86	146°/7	74.0	10.2	14.4	75.0	10.4	14.6
3	C <sub>13</sub> H <sub>22</sub> N <sub>2</sub>	84	164°/15	73.5	10.9	13.4	75.7	10.7	13.6
4	C <sub>14</sub> H <sub>24</sub> N <sub>2</sub>	72	182°/20	75.8	10.9	12.5	76.4	10.9	12.7
5	C <sub>15</sub> H <sub>26</sub> N <sub>2</sub>	85	219°/33	77.3	10.8	11.9	76.9	11.1	12.0

\* All the compounds are colourless or pale yellow, basic, water-soluble oils.

TABLE 3. ω-p-Aminophenylalkylamines (V).

n	Compound	Yield (%)	M. p. or b. p./mm.	Found (%)			Formula	Required (%)		
				C	H	N		C	H	N
3	Base <sup>a</sup>	80	179—182°/17	66.3	7.8	11.9	C <sub>12</sub> H <sub>18</sub> O <sub>2</sub> N <sub>2</sub>	66.7	7.7	12.0
	NN'-Ac <sub>2</sub> <sup>b, c</sup>		141—142							
	NN'-Bz <sub>2</sub> <sup>b, d</sup>		171—173							
4	Base <sup>a</sup>	63	176—178/13	67.6	8.2	10.9	C <sub>14</sub> H <sub>20</sub> O <sub>2</sub> N <sub>2</sub>	67.7	8.1	11.3
	NN'-Ac <sub>2</sub> <sup>b, c</sup>		154—155							
	NN'-Bz <sub>2</sub> <sup>b, d</sup>		224—225							
5	Base <sup>a</sup>	86	140—142/0.5	77.7	6.8	7.3	C <sub>16</sub> H <sub>24</sub> O <sub>2</sub> N <sub>2</sub>	77.7	6.7	7.3
	NN'-Ac <sub>2</sub> <sup>b, c</sup>		148—149°							
	NN'-Bz <sub>2</sub> <sup>b, d</sup>		197—200/15							
6	Base <sup>a</sup>	73	142	69.9	8.9	9.9	C <sub>18</sub> H <sub>26</sub> O <sub>2</sub> N <sub>2</sub>	69.6	8.7	10.2
	NN'-Ac <sub>2</sub> <sup>b, c</sup>		179—181							
	NN'-Bz <sub>2</sub> <sup>b, d</sup>		77.8 7.0 7.1							

<sup>a</sup> Cf. Müller, *Angew. Chem.*, 1949, **61**, 179; Patrick, McBee, and Hass, *J. Amer. Chem. Soc.*, 1946, **68**, 1153. <sup>b</sup> Needles. <sup>c</sup> From H<sub>2</sub>O. <sup>d</sup> From EtOH. <sup>e</sup> Cryst. <sup>f</sup> Plates. <sup>g</sup> From aq. EtOH.

of the salt (I; R = R' = R'' = Et; n = 2) the calculated quantity of sodium carbonate was used; reaction was much slower than in the corresponding trimethyl series. For the salts (I; R = R' = R'' = Et; n = 3—6) it was essential to use 50% excess of sodium carbonate and to reflux the mixture until sodium carbonate was no longer present (50—100 hr.) to avoid contamination of the product with amine hydriodides. The compound

<sup>15</sup> Zemplen, Csürös, Gerecs, and Aczel, *Ber.*, 1928, **61**, 2491.

<sup>16</sup> Beilstein and Kuhlberg, *Annalen*, 1875, **163**, 132.

<sup>17</sup> Van der Scheer, *J. Amer. Chem. Soc.*, 1934, **56**, 744.

(I; R = R' = R'' = Et;  $n = 1$ ) could not be prepared by treating *NN*-diethyl-4-diethylaminobenzylamine with ethyl iodide, only tetraethylammonium iodide being isolated from the gummy product.

TABLE 4. 4-Alkylbenzene-1:  $\omega$ -bis(trialkylammonium iodides) (I).

n	R	R'	R''	Form	M. p.	Found (%)		Formula	Required (%)	
						N	I		N	I
0	Me	Me	Me	Plates <sup>a</sup>	>250°	6.1	56.2	C <sub>15</sub> H <sub>22</sub> N <sub>2</sub> I <sub>2</sub>	6.3	56.7
1	Me	Me	Me	Needles <sup>a</sup>	>250	6.1	54.8	C <sub>15</sub> H <sub>24</sub> N <sub>2</sub> I <sub>2</sub>	6.1	55.0
2	Me	Me	Me	— <sup>b</sup>	255	6.0	53.1	C <sub>16</sub> H <sub>26</sub> N <sub>2</sub> I <sub>2</sub>	5.9	53.4
3	Me	Me	Me	Needles <sup>c</sup>	175—180 *	5.6	51.9	C <sub>16</sub> H <sub>28</sub> N <sub>2</sub> I <sub>2</sub>	5.7	51.8
4	Me	Me	Me	— <sup>d</sup>	190—195	5.5	50.1	C <sub>16</sub> H <sub>30</sub> N <sub>2</sub> I <sub>2</sub>	5.6	50.4
5	Me	Me	Me	— <sup>d</sup>	~150 *	5.4	49.3	C <sub>17</sub> H <sub>32</sub> N <sub>2</sub> I <sub>2</sub>	5.4	49.0
6	Me	Me	Me	— <sup>e</sup>	~125 *	5.1	47.4	C <sub>18</sub> H <sub>34</sub> N <sub>2</sub> I <sub>2</sub>	5.3	47.7
2	Me	Me	Et	Needles <sup>d</sup>	200 *	5.5	50.9	C <sub>16</sub> H <sub>30</sub> N <sub>2</sub> I <sub>2</sub>	5.6	50.4
3	Me	Me	Et	— <sup>d</sup>	185 *	5.4	48.7	C <sub>17</sub> H <sub>32</sub> N <sub>2</sub> I <sub>2</sub>	5.4	49.0
4	Me	Me	Et	— <sup>d</sup>	155—158 *	5.2	47.4	C <sub>18</sub> H <sub>34</sub> N <sub>2</sub> I <sub>2</sub>	5.3	47.7
5	Me	Me	Et	— <sup>f</sup>	—	—	—	C <sub>18</sub> H <sub>36</sub> N <sub>2</sub> I <sub>2</sub>	—	—
2	Me	Et	Et	— <sup>d</sup>	190 *	5.4	47.7	C <sub>18</sub> H <sub>34</sub> N <sub>2</sub> I <sub>2</sub>	5.3	47.7
3	Me	Et	Et	— <sup>d</sup>	185 *	5.2	46.5	C <sub>18</sub> H <sub>36</sub> N <sub>2</sub> I <sub>2</sub>	5.1	46.5
4	Me	Et	Et	— <sup>g</sup>	176 *	5.0	45.5	C <sub>20</sub> H <sub>38</sub> N <sub>2</sub> I <sub>2</sub>	5.0	45.4
5	Me	Et	Et	— <sup>f</sup>	—	—	—	C <sub>21</sub> H <sub>40</sub> N <sub>2</sub> I <sub>2</sub>	—	—
2	Et	Et	Et	— <sup>d</sup>	187 *	5.1	45.3	C <sub>20</sub> H <sub>38</sub> N <sub>2</sub> I <sub>2</sub>	5.0	45.4
3	Et	Et	Et	— <sup>h</sup>	193 *	5.1	44.1	C <sub>21</sub> H <sub>40</sub> N <sub>2</sub> I <sub>2</sub>	4.9	44.3
4	Et	Et	Et	— <sup>i</sup>	~183 *	4.7	43.0	C <sub>22</sub> H <sub>42</sub> N <sub>2</sub> I <sub>2</sub>	4.8	43.2
5	Et	Et	Et	— <sup>i</sup>	—	4.4	41.0	C <sub>22</sub> H <sub>44</sub> N <sub>2</sub> I <sub>2</sub>	4.7	42.2
6	Et	Et	Et	— <sup>h</sup>	—	4.2	40.5	C <sub>24</sub> H <sub>46</sub> N <sub>2</sub> I <sub>2</sub>	4.6	41.2

\* With decomp.

<sup>a</sup> From aq. EtOH. <sup>b</sup> From H<sub>2</sub>O. <sup>c</sup> From MeOH. <sup>d</sup> From EtOH. <sup>e</sup> From MeOH-EtOH.

<sup>f</sup> Gum, characterised as cryst. 4 : 4'-diaminostilbene-2 : 2'-disulphonate (cf. ref. 18). <sup>g</sup> From EtOH-COMe<sub>2</sub>-EtOAc. <sup>h</sup> From EtOH-EtOAc. <sup>i</sup> From EtOH-COMe<sub>2</sub>.

A glass was obtained on attempting to prepare the bisquaternary salt (I; R = Me, R' = R'' = Et;  $n = 1$ ) from 4-diethylamino-*NN*-diethylbenzylamine with methyl iodide. This diamine was obtained by lithium aluminium hydride reduction of the thioamide prepared by heating *p*-diethylaminobenzaldehyde with sulphur and diethylamine at 170°. For homologous thioamides similar routes were unsatisfactory, so required  $\omega$ -diethylamino-1-*p*-diethylaminophenylalkanes were prepared by conversion of the iodides (I; R = R' = R'' = Et;  $n = 2-5$ ) into the chlorides which were distilled to give the crude diamines as colourless oils (contaminated with halogen-containing impurities): the compounds were not obtained analytically pure but with methyl iodide furnished the desired bisquaternary salts (I; R = Me, R' = R'' = Et;  $n = 2-6$ ). The compounds where  $n = 2-4$  were obtained crystalline, but those where  $n = 5$  and 6 were gums. The product ( $n = 5$ ) was converted into the crystalline 4 : 4'-diaminostilbene-2 : 2'-disulphonate.<sup>18</sup>

#### EXPERIMENTAL

*Tetra-N-methyl-p-phenylenediamine*.—*p*-Phenylenediamine (67 g.) was added gradually to stirred, ice-cooled 90% formic acid (200 c.c.) at 10–20°. The mixture was then warmed to 65° and 40% aqueous formaldehyde (280 c.c.) was added during 30 min. the temperature rising to 70°. Stirring was then stopped and the mixture heated at 88° (steam-bath) for 2 hr., cooled, basified with sodium hydroxide solution, and extracted with ether. The combined extracts were dried (Na<sub>2</sub>SO<sub>4</sub>) and fractionated. The fraction, b. p. 150–160°/27 mm. (9 g.), partly solidified and when drained gave the pale yellow ditertiary base (6 g., 5.5%), m. p. 50–51° (Meyer<sup>7</sup> gives m. p. 51°).

A solution of methyl iodide (50 c.c.) and the base (9.5 g.) in ethanol (125 c.c.) deposited during 30 min. *p*-dimethylaminophenyltrimethylammonium iodide (90%), m. p. ca. 265° (decomp.) (from aqueous ethanol) (Found: I, 41.7. Calc. for C<sub>11</sub>H<sub>18</sub>N<sub>2</sub>I: I, 41.5%) (Pinnow and Pistov<sup>8</sup> give m. p. 265°). The crude iodide (12 g.) was heated with ethylene glycol (90 c.c.) and methyl iodide (30 c.c.) in a sealed tube at 100° for 72 hr. (heating for shorter periods gave a product

<sup>18</sup> Leeds and Slack, *J.*, 1956, 3941.

contaminated with the starting material). The resulting dark brown solid was freed from iodine by washing it with ethylene glycol, and distilling its solution in water with steam. The solution was then evaporated (15 mm.) to dryness, and the *p*-phenylene bis(trimethylammonium iodide) was triturated with acetone (see Table 4).

*p*-Dimethylaminophenethylamine.— $\beta$ -*p*-Dimethylaminophenylpropionic acid<sup>18</sup> (7.5 g.), suspended in dry benzene (80 c.c.), was treated with thionyl chloride (15 c.c.) gradually with shaking. After 65 hr., the solvent and excess of thionyl chloride were evaporated at <30°/15 mm. The residue was dissolved in acetone (20 c.c.) and added during 10 min. to a stirred solution of sodium azide (5.2 g.) in water (40 c.c.) and acetone (15 c.c.) at 5–10°. Stirring was continued at room temperature for 15 min., and the mixture was extracted with benzene. The deep brown extracts were dried (CaCl<sub>2</sub>), warmed on the steam-bath for 30 min., boiled for 1.5 hr. with concentrated hydrochloric acid (15 c.c.) and water (15 c.c.), and then evaporated to dryness (15 mm.). The dark semi-solid products from six such experiments were combined and dissolved in water, the solution was basified with sodium hydroxide solution and distilled with steam, and the distillate was acidified with hydrochloric acid and evaporated to dryness at 15 mm. The base was liberated from a concentrated solution of the dihydrochloride with solid sodium hydroxide and extraction with ether gave the amine (17.8 g., 47%), b. p. 152°/13 mm. The *N*-benzoyl derivative, crystallised in needles [from benzene–light petroleum (b. p. 80–100°)], m. p. 133° (Buck<sup>19</sup> gives m. p. 130°); the *phenylureido-derivative* formed plates (from ethanol), m. p. 158–159° (Found: C, 72.1; H, 7.4; N, 14.6. C<sub>17</sub>H<sub>21</sub>ON<sub>3</sub> requires C, 72.1; H, 7.4; N, 14.8%).

$\omega$ -*p*-Nitrophenyl-*n*-alkane-1-carboxyamides.—The  $\omega$ -*p*-nitrophenyl-*n*-alkanoic acid<sup>14, 17</sup> (0.2–0.4 mole), dissolved or suspended in dry benzene (500–1000 c.c.), was treated with phosphorus pentachloride (0.25–0.50 mole). After being kept at room temperature overnight, the resulting solution was gradually added to stirred, ice-cooled, concentrated aqueous ammonia (750–1500 c.c.) so that the temperature did not rise above 10°. Next day the crude carboxamide was filtered off, washed with water, and dried. This material was used in preparations of the corresponding cyanides. Pure samples of the following carboxyamides were prepared:  $\gamma$ -*p*-nitrophenylbutyramide (75%), needles (from water), m. p. 135–137° (Found: C, 58.0; H, 6.0; N, 13.5. C<sub>10</sub>H<sub>12</sub>O<sub>2</sub>N<sub>2</sub> requires C, 57.7; H, 5.8; N, 13.5%),  $\delta$ -*p*-nitrophenylvaleramide (96%), slightly yellow needles (from benzene), m. p. 127–128° (Found: C, 59.6; H, 6.5; N, 12.5. C<sub>11</sub>H<sub>14</sub>O<sub>2</sub>N<sub>2</sub> requires C, 59.5; H, 6.3; N, 12.6%), and 6-*p*-nitrophenylhexanamide (90%), pale yellow needles (from benzene), m. p. 120–122° (Found: C, 61.4; H, 6.8; N, 11.6. C<sub>12</sub>H<sub>16</sub>O<sub>2</sub>N<sub>2</sub> requires C, 61.0; H, 6.8; N, 11.9%).

$\omega$ -*p*-Nitrophenyl-*n*-alkyl Cyanides (VI; *n* = 1–5).—The following were prepared by refluxing the appropriate amide (0.1–0.4 mole) with thionyl chloride (50–200 c.c.) for 2 hr. and fractionating the mixture: 3-*p*-nitrophenylpropyl cyanide (89%), b. p. 162–164°/0.5 mm. (Found: C, 63.0; H, 5.3; N, 15.0. C<sub>10</sub>H<sub>10</sub>O<sub>2</sub>N<sub>2</sub> requires C, 63.2; H, 5.3; N, 14.7%), 4-*p*-nitrophenylbutyl cyanide (80%), yellowish rods (from ethanol), m. p. 43–44°, b. p. 188–190°/0.5 mm. (Found: C, 64.9; H, 6.0; N, 13.7. C<sub>11</sub>H<sub>12</sub>O<sub>2</sub>N<sub>2</sub> requires C, 64.7; H, 5.9; N, 13.7%), and 5-*p*-nitrophenylpentyl cyanide (86%), b. p. 194°/0.5 mm. (Found: C, 66.0; H, 6.5; N, 13.0. C<sub>12</sub>H<sub>14</sub>O<sub>2</sub>N<sub>2</sub> requires C, 66.1; H, 6.4; N, 12.8%).

2-*p*-Nitrophenethyl cyanide (VI; *n* = 2) was prepared by nitrating phenethyl cyanide (Henley and Turner<sup>20</sup>) as described by Zemplén *et al.*<sup>15</sup> Hydrolysis with boiling hydrochloric acid gave  $\beta$ -*p*-nitrophenylpropionic acid, m. p. 164° (Beilstein and Kuhlberg<sup>16</sup> give m. p. 163–164°).

4-*p*-Aminophenylbutyl Cyanide.—4-*p*-Nitrophenylbutyl cyanide (30 g.) in methanol (300 c.c.) was reduced with hydrogen at 30°/60 lb. per sq. in. in presence of Adams catalyst (2%) in 35 min. and afforded the new cyanide (18 g., 74%), b. p. 162–164°/0.5 mm. (Found: C, 75.5; H, 8.1; N, 16.2. C<sub>11</sub>H<sub>14</sub>N<sub>2</sub> requires C, 75.9; H, 8.1; N, 16.1%). The *N*-benzoyl derivative, platelets (from ethanol), had m. p. 145–146° (Found: C, 77.5; H, 6.5; N, 9.9. C<sub>18</sub>H<sub>18</sub>ON<sub>2</sub> requires C, 77.7; H, 6.5; N, 10.1%).

4-*p*-Dimethylaminophenylbutyl Cyanide.—A mixture of the above amino-nitrile (8.7 g., 0.05 mole), sodium carbonate (5.5 g., 0.055 mole), methyl iodide (20 c.c.), and methanol (50 c.c.) was refluxed for 3 hr. to give the required cyanide as a light yellow oil (6.8 g., 68%), b. p. 214–216°/20 mm. (Found: C, 77.1; H, 8.8; N, 13.9. C<sub>13</sub>H<sub>18</sub>N<sub>2</sub> requires C, 77.2; H, 8.9; N,

<sup>19</sup> Buck, *J. Amer. Chem. Soc.*, 1933, **55**, 2596.

<sup>20</sup> Henley and Turner, *J.*, 1931, 1183.

13.9%). The yellow *picrate*, from ethanol, had m. p. 96—98° (Found: C, 52.5; H, 5.1; N, 16.0.  $C_{18}H_{21}O_7N_3$  requires C, 52.9; H, 4.9; N, 16.2%).

*δ-p-Dimethylaminophenylvaleric Acid.*—(a) 4-*p*-Dimethylaminophenylbutyl cyanide (6 g.) with potassium hydroxide (6 g.) in ethanol (12 c.c.)–water (18 c.c.) at the b. p. (6 hr.) gave the *acid* (4.6 g., 70%), which crystallised from ethanol (charcoal) as a pinkish powder, m. p. 99—100° (Found: C, 71.0; H, 9.0; N, 6.3.  $C_{15}H_{19}O_2N$  requires C, 70.6; H, 8.6; N, 6.3%). (b) A mixture of *δ-p*-dimethylaminophenyl-*NN*-dimethylthiovaleramide (1.7 g.), potassium hydroxide (2 g.), and water (20 c.c.) was refluxed for 10 hr., shaken with charcoal, and filtered, and adjusted to pH 6 by 2*N*-hydrochloric acid. The precipitated acid was dissolved in saturated aqueous sodium hydrogen carbonate, the turbid solution was shaken with charcoal and filtered, and 2*N*-hydrochloric acid was added to the filtrate to pH 6. The solution gradually deposited colourless needles (50 mg.) of the acid, m. p. 99—100°, identical with that prepared by method (a).

*ω-p-Dimethylaminophenyl-n-alkane-1-(NN-dimethylthiocarboxyamides)* (III; *n* = 1—5; Table 1).—A mixture of *p*-dimethylaminobenzaldehyde (or the appropriate *n*-alkyl *p*-dimethylaminophenyl ketone<sup>13</sup>) (0.2 mole), sulphur (6.4 g.), and anhydrous dimethylamine (12 c.c.) was heated in a thick-walled tube (12" × 1") at 170—180° (bath-temp.) for 3—4 hr. Crude thioamide (III; *n* = 1) was obtained as a dark solid which was purified by crystallisation. In the preparation of the amides (III; *n* = 2 and 3) the cold mixture was a dark brown, malodorous semi-solid mass. This was triturated with ether to give the crude product which was purified by crystallisation. In the case of products (III; *n* = 4 and 5) the mixture, a malodorous dark red oil, was dissolved in ether, the solution was extracted with insufficient 2*N*-hydrochloric acid to extract all the basic material, and the extracts were partly neutralised with dilute sodium carbonate. Resinous material was filtered off after addition of charcoal, and the filtrate was basified with sodium carbonate. The liberated dark oil was extracted with ether, and the extracts were shaken with charcoal and magnesium sulphate and then evaporated to dryness. The residual dark reddish-brown oil was triturated with ether at *ca.* –10° to yield the crude product which was purified by crystallisation.

1-*ω-Dimethylamino-p-dimethylaminophenylalkanes* (IV; *n* = 1—5; Table 2).—The appropriate thioamide (0.04—0.06 mole) in ether (500—1000 c.c.) was added during 30—60 min. to a stirred suspension of finely powdered lithium aluminium hydride (0.05—0.07 mole) in ether (100—150 c.c.). After the mixture had been stirred for a further 1 hr., water was added cautiously and the mixture treated with 2*N*-hydrochloric acid. The acid extracts were basified with aqueous sodium hydroxide and distilled with steam, and the bases were isolated as described for *p*-dimethylaminophenethylamine.

4-*Alkylbenzene-1 : ω-bis(trimethylammonium Iodides)* (I; R = R' = R'' = Me; *n* = 0—6; Table 4).—The compounds (I; *n* = 3—5) were prepared by treatment of the appropriate 1-dimethylamino-*ω-p*-dimethylaminophenylalkane (3—5 g.) in methanol (20—100 c.c.) with methyl iodide (10 c.c.). The compounds (I; *n* = 1 and 2) were prepared by adding methyl iodide (10 c.c.) to the 1-amino-*ω-p*-dimethylaminophenylalkane (0.1 mole) in methanol (50 c.c.). When the exothermic reaction had subsided the mixture was refluxed with sodium carbonate (10.6 g., 0.1 mole), methyl iodide (10 c.c.), and methanol (25 c.c.). The compound (I; *n* = 6) was prepared by boiling 6-*p*-aminophenylhexylamine (3.8 g., 0.02 mole) with methyl iodide (25 c.c.), sodium carbonate (4.6 g.; 0.044 mole) and methanol (100 c.c.) for 18 hr. The clear solution was evaporated at 15 mm., and the residual solid was triturated with acetone, giving the crude bisquaternary ammonium iodide. The compound (I; *n* = 2) was also prepared by gradually adding methyl iodide (300 c.c., 4.8 moles) to *p*-aminophenethylamine (54 g., 0.4 mole) and sodium carbonate (85 g., 0.8 mole) in methanol (750 c.c.). After the vigorous exothermic reaction had subsided the mixture was refluxed for 10 hr. The crude product (155 g., 80%) had m. p. 246—248° (decomp.). In all cases the compounds were purified by recrystallisation. The compound (I; *n* = 3) (66 g., 88%), m. p. *ca.* 175° (decomp.), was similarly prepared by refluxing 3-*p*-aminophenylpropylamine (23 g., 0.15 mole), sodium carbonate (35.2 g.; 0.31 mole), and methyl iodide (75 c.c.) in methanol (400 c.c.) for 7 hr.

4-*Alkylbenzene-1 : ω-bis(ethyltrimethylammonium Iodides)* (I; R = R' = Me, R'' = Et; *n* = 2—5; Table 4).—The appropriate 1-dimethylamino-*ω-p*-dimethylaminophenylalkane (2.5—5.0 g.) in ethanol (10 c.c.) was refluxed with ethyl iodide (10 c.c.) for 2 hr. On cooling, only the compound (I; *n* = 2) separated in a form suitable for crystallisation. For the other compounds, the solvent and ethyl iodide were evaporated and the residual brown gum was

trituated with acetone. Compounds (I;  $n = 3$  and  $4$ ) were thus obtained crystalline and were purified by crystallisation, but compound (I;  $n = 5$ ) was a gum which was converted into the 4 : 4'-diaminostilbene-2 : 2'-disulphonate as described in Part II.<sup>18</sup>

1- $\omega$ -*p*-Aminophenylalkylamines (V;  $n = 2-6$ ) (Table 3).—The compounds were prepared by catalytic reduction of the nitro-cyanides (VI;  $n = 1-5$ ) (0.15–0.40 mole) in methanol (150–400 c.c.) in the presence of Adams catalyst (2.5%) at 35°/70–80 lb. per sq. in. When reduction of the nitro-group was complete, the platinum was filtered off, anhydrous ammonia was introduced, and reduction of the cyano-group was effected in presence of Raney nickel (10%) at 55–70°/500–900 lb. per sq. in. After filtration and evaporation of the solvent, the residual oil was distilled, to give the diamine. The diamines distilled as colourless oils which crystallised and rapidly became brown in air. As they reacted readily with atmospheric carbon dioxide, the bases were not analysed but were characterised as their crystalline *NN'*-diacetyl and/or -dibenzoyl derivatives.

4-Alkylbenzene-1 :  $\omega$ -bis(triethylammonium Iodides) (I;  $R = R' = R'' = Et$ ;  $n = 2-6$ ; Table 4).—The compound (I;  $n = 2$ ) was obtained on refluxing a mixture of *p*-aminophenethylamine (0.03 mole), sodium carbonate (6.4 g., 0.06 mole), ethanol (20 c.c.), and ethyl iodide (25 c.c.) for 20 hr. The clear solution, on cooling, deposited 4-ethylbenzene-1 : 2'-bis(triethylammonium iodide) which was recrystallised. When the compound (I;  $n = 3$ ) was prepared in a similar way, the cooled reaction mixture was treated with acetone and kept at 0°. The solid, which separated, consisted of the bisquaternary salt mixed with amine hydriodides. The impurities were removed by repeated crystallisation from ethanol-ethyl acetate. Further quantities of the compound (I;  $n = 3$ ) and of the compounds (I;  $n = 4-6$ ) were prepared by refluxing the appropriate diamine (0.025–0.100 mole) with ethyl iodide (25–75 c.c.), ethanol (75 c.c.), and 50% excess of sodium carbonate (0.075–0.300 mole) until a clear solution was obtained (50–100 hr.). The solution was then evaporated at 15 mm. and the residual solid, which was sticky only in the case of compound (I;  $n = 4$ ), was treated with acetone to yield the crude bisquaternary salt. In the preparation of the compounds (I;  $n = 5$  and  $6$ ) the solid was completely soluble in acetone, but solid material was obtained on keeping the solution at 0° with or without the addition of ethyl acetate.

An attempt was made to prepare the compound (I;  $n = 1$ ) by refluxing *NN*-diethyl-4-diethylaminobenzylamine (2.5 g.) with ethyl iodide (10 c.c.) for 24 hr. Ethanol and excess of ethyl iodide were evaporated and the residual brown gum was trituated with acetone (the acetone liquors yielded only gum), giving colourless crystals (1 g.), m. p. >260°. These were shown to be tetraethylammonium iodide (Found: I, 49.2. Calc. for  $C_8H_{20}NI$ : I, 49.4%) by conversion into the picrate, deep yellow needles (from ethanol), m. p. 248–249°, undepressed by mixing with an authentic sample, m. p. 251–252°.

4-Diethylamino-*NN*-diethylbenzylamine.—*p*-diethylaminobenzaldehyde (35.4 g., 0.2 mole), sulphur (6.4 g., 0.2 g.-atom), and diethylamine (14 c.c.) was heated at 170–180° for 3 hr. The thioamide was obtained as pale yellow platelets (11%), m. p. 86–88°, from light petroleum (b. p. 60–80°) (Found: C, 68.4; H, 9.1; N, 10.4.  $C_{15}H_{24}N_2S$  requires C, 68.2; H, 9.1; N, 10.6%). Reduction with lithium aluminium hydride as described previously gave 4-diethylamino-*NN*-diethylbenzylamine (84%), b. p. 169°/7 mm. (Found: C, 76.9; H, 11.1; N, 11.5.  $C_{15}H_{26}N_2$  requires C, 76.9; H, 11.1; N, 12.0%).

For the preparation of the other bisdiethylamino-compounds, the appropriate 1-*n*-alkylbenzene-4 :  $\omega$ -bis(triethylammonium iodide) (0.01–0.07 mole) in water (250–1000 c.c.) was added to a stirred suspension of freshly prepared silver chloride (0.2 mole) in hot water (500 c.c.). The mixture was heated on the steam-bath and stirred for 2 hr., then filtered, and the combined filtrate and washings were shaken with charcoal. After removal of charcoal the filtrate was evaporated at 15 mm. and the residue of bisquaternary chloride was distilled *in vacuo*, to give the 1-diethylamino- $\omega$ -*p*-diethylaminophenylalkane. The products, after distillation, were contaminated with halogen-containing material (Beilstein test) and were not pure. The following were thus prepared: 1-diethylamino-2-*p*-diethylaminophenylethane (16%), b. p. 170–180° (bath-temp.)/17 mm., 1-diethylamino-3-*p*-diethylaminophenylpropane (29%), b. p. 194–196°/10 mm., 1-diethylamino-4-*p*-diethylaminophenylbutane (26%), b. p. 210–213° (bath-temp.)/10 mm., and 1-diethylamino-5-*p*-diethylaminophenylpentane (35%), b. p. 235–240° (bath-temp.)/18 mm.

4-Alkylbenzene-1 :  $\omega$ -bis(diethylmethylammonium Iodides) (I;  $R = Me$ ,  $R' = R'' = Et$ ;  $n = 2-5$ ; Table 4).—A solution of the 1-diethylamino- $\omega$ -*p*-diethylaminophenylalkane (2.5–4.5 g.)

in methanol (10—20 c.c.) was refluxed with methyl iodide (10—15 c.c.) for 24 hr. Evaporation left a brownish gum. Trituration with acetone gave the crystalline compounds (I;  $n = 2-4$ ) but the remaining gum would not solidify. This compound (I;  $n = 5$ ) was converted into the 4 : 4'-diaminostilbene-2 : 2'-disulphonate as described in Part II.<sup>18</sup>

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