

[CONTRIBUTION FROM DEFENCE RESEARCH CHEMICAL LABORATORIES]

**N- $\beta$ -Nitraminoethyl-N'-aryl-N''-nitroguanidines<sup>1</sup>**

By A. F. MCKAY, W. G. HATTON AND G. W. TAYLOR

RECEIVED OCTOBER 6, 1952

Arylamines combine with 1-nitro-2-nitramino-2-imidazoline to give the corresponding N- $\beta$ -nitraminoethyl-N'-aryl-N''-nitroguanidines. N- $\beta$ -Nitraminoethyl-N'-*p*-anisyl-N''-nitroguanidine on treatment with acetyl chloride in glacial acetic acid yields 1-nitro-2-*p*-anisylamino-2-imidazolinium chloride and N- $\beta$ -chloroethyl-N'-*p*-anisylurea as the chief products. These reactions are discussed.

Ammonia and aliphatic amines combine with 1-nitro-2-nitramino-2-imidazolines to give acyclic nitroguanidine derivatives.<sup>2,3</sup> This reaction has now been extended to include arylamines. Arylamines and 1-nitro-2-nitramino-2-imidazoline refluxed in aqueous ethanol give in the majority of preparations almost quantitative yields of the corresponding N- $\beta$ -nitraminoethyl-N'-aryl-N''-nitroguanidines (I). Some of these derivatives are listed along with their properties in Table I.

of the reaction by the decomposition of the -NHNO<sub>2</sub> group. 1-Nitro-2-*p*-acetamidophenylamino-2-imidazoline (or its tautomer 1-nitro-2-*p*-acetamidophenylimino-2-imidazolidine) with acetyl chloride in glacial acetic acid gives the original compound as its hydrochloride. Thus ring opening does not occur under anhydrous conditions. On the other hand, aqueous hydrochloric acid readily converts 1-nitro-2-*p*-acetamidophenylamino-2-imidazoline into N- $\beta$ -nitraminoethyl-N'-*p*-acetamidophenylurea.<sup>4</sup>

TABLE I  
NO<sub>2</sub>NHCH<sub>2</sub>CH<sub>2</sub>NHC(NR)NHNO<sub>2</sub>

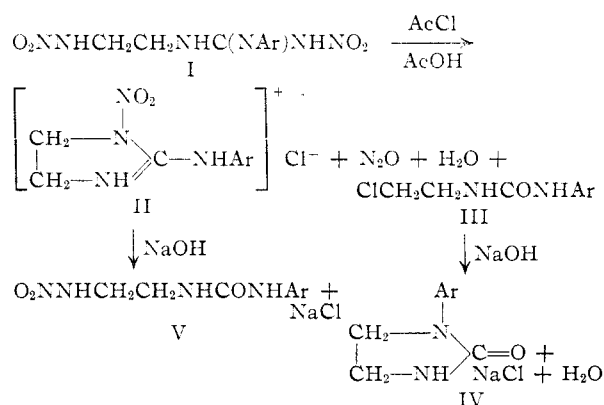
R	M.p., °C. <sup>a</sup>	Yield, %	Formula	Carbon, %		Hydrogen, %		Nitrogen, %	
Phenyl	139.5–140.5	96.0	C <sub>9</sub> H <sub>12</sub> N <sub>6</sub> O <sub>4</sub>	40.20	40.49	4.48	4.67	31.40	31.60
<i>p</i> -Tolyl	163.5–164	89.6	C <sub>10</sub> H <sub>14</sub> N <sub>6</sub> O <sub>4</sub>	42.55	42.74	4.96	5.19	29.78	30.02
<i>o</i> -Tolyl	108–109	51.2	C <sub>10</sub> H <sub>14</sub> N <sub>6</sub> O <sub>4</sub>	42.55	42.90	4.96	5.07	29.78	29.92
<i>p</i> - <i>s</i> -Amylphenyl	137–138	85.3	C <sub>14</sub> H <sub>22</sub> N <sub>6</sub> O <sub>4</sub>	49.71	49.91	6.56	6.66	24.81	25.16
<i>p</i> -Hydroxyphenyl	172–173	88.4	C <sub>9</sub> H <sub>12</sub> N <sub>6</sub> O <sub>5</sub>	38.01	38.12	4.22	4.13	29.58	29.87
<i>p</i> -Anisyl	176.5–177	100	C <sub>10</sub> H <sub>14</sub> N <sub>6</sub> O <sub>5</sub>	40.20	40.57	4.69	4.80	28.20	28.20
<i>o</i> -Anisyl	124–125	65.5	C <sub>10</sub> H <sub>14</sub> N <sub>6</sub> O <sub>5</sub>	40.20	40.70	4.69	4.79	28.20	28.50
<i>p</i> -Phenetyl	134–135.5	85.0	C <sub>11</sub> H <sub>16</sub> N <sub>6</sub> O <sub>5</sub>	42.30	42.39	5.13	5.28	26.90	27.50
<i>m</i> -Phenetyl	135–136.5	90.7	C <sub>11</sub> H <sub>16</sub> N <sub>6</sub> O <sub>5</sub>	42.30	42.26	5.13	5.34	26.90	26.91
<i>p</i> -Acetamidophenyl	185.5	99.5	C <sub>11</sub> H <sub>16</sub> N <sub>7</sub> O <sub>5</sub>	40.60	40.76	4.61	4.84	30.15	30.15
<i>p</i> -Chlorophenyl	155–156	80.0	C <sub>9</sub> H <sub>11</sub> ClN <sub>6</sub> O <sub>4</sub>	35.70	35.75	3.64	3.80	X, 11.63	11.84
<i>m</i> -Chlorophenyl	124–125	77.9	C <sub>9</sub> H <sub>11</sub> ClN <sub>6</sub> O <sub>4</sub>	35.70	35.80	3.64	3.80	27.78	28.06
<i>p</i> -Bromophenyl	153–153.5	89.7	C <sub>9</sub> H <sub>11</sub> BrN <sub>6</sub> O <sub>4</sub>	31.10	31.26	3.17	3.31	X, 23.06	23.36
Benzyl	112.5–113	95.9	C <sub>10</sub> H <sub>14</sub> N <sub>6</sub> O <sub>4</sub>	42.55	42.57	4.96	5.04	29.78	29.81

<sup>a</sup> All the compounds decompose at the recorded temperatures.

N- $\beta$ -Nitraminoethyl-N'-*p*-anisyl-N''-nitroguanidine (I, Ar = *p*-anisyl) with acetyl chloride in glacial acetic acid evolved nitrous oxide. The products consisted of a mixture of 1-nitro-2-aryl-amino-2-imidazolinium chloride (II, Ar = *p*-anisyl) and N- $\beta$ -chloroethyl-N'-*p*-anisylurea (III, Ar = *p*-anisyl). No N- $\beta$ -chloroethyl-N'-*p*-anisyl-N''-nitroguanidine could be isolated from the products. Thus under the conditions of the reaction cyclization readily occurs. The main difference between the reactions of N- $\beta$ -nitraminoethyl-N'-*p*-anisyl-N''-nitroguanidine and N- $\beta$ -nitraminoethyl-N'-alkyl-N''-nitroguanidines<sup>3</sup> with acetyl chloride is in the former case the corresponding N- $\beta$ -chloroethylurea is obtained in fair yield. This is thought to be due to the influence of the aryl substituent. The formation of the urea derivative is considered to be the result of acid hydrolysis of the 1-nitro-2-arylamino-2-imidazoline.<sup>3</sup> The water necessary for this hydrolysis is supplied at the site

Aqueous hydrochloric acid also converts 1-nitro-2-nitramino-2-imidazoline into N- $\beta$ -chloroethyl-N'-nitroreua.<sup>5</sup>

N- $\beta$ -Chloroethyl-N'-*p*-anisylurea (III, Ar = *p*-anisyl) was identified by cyclization to the known 1-*p*-anisyl-2-imidazolidone (IV)<sup>6</sup> and synthesis from



(1) Issued as D. R. C. L. Report No. 105.

(2) (a) A. F. McKay, J. P. Picard and P. E. Brunet, *Can. J. Chem.*, **29**, 746 (1951); (b) A. F. McKay and C. Sandorfy, *ibid.*, **31**, 42 (1953).

(3) A. F. McKay and W. G. Hatton, *THIS JOURNAL*, **75**, 963 (1953).

(4) A. F. McKay, *J. Org. Chem.*, **16**, 1846 (1951).

(5) A. F. McKay, *et al.*, to be published.

(6) A. F. McKay, W. R. R. Park and S. J. Viron, *THIS JOURNAL*, **72**, 3659 (1950).

*p*-anisyl isocyanate and  $\beta$ -chloroethylamine. When N- $\beta$ -chloroethyl-N'-*p*-anisylurea was separated from 1-nitro-2-*p*-anisylamino-2-imidazolium chloride with cold 10% sodium hydroxide solution, 1-nitro-2-*p*-anisylamino-2-imidazoline (II) went into solution leaving behind the urea. On acidification of the alkaline filtrate the hydrolysis product, N- $\beta$ -nitraminoethyl-N'-anisylurea (V),<sup>7</sup> of compound II was obtained.

N- $\beta$ -Nitraminoethyl-N'-phenyl-N"-nitroguanidine (I, Ar = phenyl) with acetyl chloride gave 1-nitro-2-phenylamino-2-imidazolium hydrochloride (II, Ar = phenyl). The latter compound was hydrolyzed to N- $\beta$ -nitraminoethyl-N'-phenylurea with 10% sodium hydroxide solution.

### Experimental<sup>8,9</sup>

**N- $\beta$ -Nitraminoethyl-N'-aryl-N"-nitroguanidines. Method A.**—Five grams (0.029 mole) of 1-nitro-2-nitramino-2-imidazoline and 1.5–2.0 mole equivalents of an arylamine were refluxed in 30 cc. of 95% ethanol for two hours. After the reaction mixture had cooled to room temperature, the crystals were removed by filtration and washed with ether. The crude product was generally quite pure but in some cases further purification was effected by crystallization from 95% ethanol. The compounds prepared by this method are described in Table I.

**Method B.**—Three grams (0.017 mole) of 1-nitro-2-nitramino-2-imidazoline and 2.7 g. (0.022 mole) of *p*-anisidine were refluxed in 25 cc. of 25% aqueous ethanol for a period of 15 minutes. The crystals were filtered from the cooled mixture and then washed with ether; yield 4.86 g. (95.2%). The crude melting point of 170–171° with decomposition was unaltered by crystallization from 95% ethanol. A mixed melting point determination with an authentic sample of N- $\beta$ -nitraminoethyl-N'-*p*-anisyl-N"-nitroguanidine prepared by method A was unchanged.

**Reaction of N- $\beta$ -Nitraminoethyl-N'-phenyl-N"-nitroguanidine with Acetyl Chloride.**—N- $\beta$ -Nitraminoethyl-N'-phenyl-N"-nitroguanidine (7.5 g., 0.028 mole) was added to a solution of 6.4 cc. (0.090 mole) of acetyl chloride, 6.0 cc. of glacial acetic acid and 8 cc. (0.085 mole) of acetic anhydride. This mixture was heated at 52–55° for two hours. The solvent and excess acetyl chloride were removed *in vacuo* leaving a semi-solid residue. This residue was transferred to a Soxhlet and extracted with ether; yield 3.2 g. (47.2%). This material melted at 165–165.9° with decomposition and it gave a positive test for chlorine. A deep green color was obtained in the Franchimont test<sup>10</sup> with dimethylaniline. After washing with 25 cc. of ethyl acetate the melting point remained constant at 169–169.6° with decomposition. A portion (510 mg., 0.002 mole) of this material treated with alcoholic picric acid solution gave 580 mg. (63.4%) of the picrate of 1-nitro-2-phenylamino-2-imidazoline which melted at 155.5° with decomposition. This melting point remained unaltered by crystallizing from 95% ethanol.

*Anal.* Calcd. for C<sub>16</sub>H<sub>13</sub>N<sub>7</sub>O<sub>9</sub>: C, 41.78; H, 2.98; N, 22.52. Found: C, 41.81; H, 3.16; N, 22.82.

The styphnate of 1-nitro-2-phenylamino-2-imidazoline was formed in the usual manner. It was obtained in 91% yield with a melting point of 159° with decomposition.

*Anal.* Calcd. for C<sub>15</sub>H<sub>13</sub>N<sub>7</sub>O<sub>10</sub>: C, 39.93; H, 2.88; N, 21.73. Found: C, 39.95; H, 3.15; N, 22.03.

One gram (0.004 mole) of 1-nitro-2-phenylamino-2-imidazoline hydrochloride (m.p. 169.6° with dec.) was dissolved in 5 cc. of 10% aqueous sodium hydroxide solution at room temperature. After the clear solution had stood for 10 minutes, it was acidified with 10% hydrochloric acid solution. The precipitated crystals were removed by filtration and washed with water; yield 635 mg. (68.8%). The melting point of 156° with decomposition was raised to 159°

with decomposition by one crystallization from 95% ethanol. The analytical values agree with the calculated for the expected N- $\beta$ -nitraminoethyl-N'-phenylurea.

*Anal.* Calcd. for C<sub>9</sub>H<sub>10</sub>O<sub>3</sub>: C, 48.20; H, 5.35; N, 25.00. Found: C, 48.64; H, 5.67; N, 24.93.

**Reaction of N- $\beta$ -Nitraminoethyl-N'-*p*-anisyl-N"-nitroguanidine with Acetyl Chloride.**—Five grams (0.0168 mole) of N- $\beta$ -nitraminoethyl-N'-*p*-anisyl-N"-nitroguanidine, 3.94 g. (0.050 mole) of acetyl chloride, 5.15 g. (0.050 mole) of acetic anhydride and 60 cc. of glacial acetic acid were placed in a three-necked flask fitted with a thermometer, stirrer and gas outlet. This mixture was heated at 40° for one hour after which gas evolution had ceased and a clear solution remained. The yellow solution was evaporated to dryness *in vacuo* and treated with absolute methanol (3 × 25 cc.). After each addition of methanol the solvent was removed *in vacuo*. The residue weighed 4.10 g. An aliquot of this residue was converted to the picrate in the usual manner. This crystalline picrate of 1-nitro-2-*p*-anisylamino-2-imidazoline melted at 150° with decomposition after crystallization from 95% ethanol.

*Anal.* Calcd. for C<sub>16</sub>H<sub>13</sub>N<sub>7</sub>O<sub>10</sub>: C, 41.28; H, 3.24; N, 21.08. Found: C, 41.05; H, 3.51; N, 21.10.

The hydrochloride of 1-nitro-2-*p*-anisylamino-2-imidazoline was converted into the styphnate in the usual manner. This yellow crystalline styphnate melted at 161° with decomposition.

*Anal.* Calcd. for C<sub>16</sub>H<sub>13</sub>N<sub>7</sub>O<sub>11</sub>: C, 39.90; H, 3.11; N, 20.38. Found: C, 40.08; H, 3.31; N, 19.94.

The remaining residue (4.0 g.) was treated with 25 cc. of 10% aqueous sodium hydroxide solution and allowed to stand at room temperature for six hours. An insoluble material was removed by filtration and washed with water; yield 1.57 g. (46.7%). The melting point of this impure N- $\beta$ -chloroethyl-N'-*p*-anisylurea (m.p. 139°) was raised to 162° by two crystallizations from 95% ethanol.

*Anal.* Calcd. for C<sub>10</sub>H<sub>13</sub>ClN<sub>2</sub>O<sub>2</sub>: C, 52.51; H, 5.69; Cl, 15.54. Found: C, 52.72; H, 5.80; Cl, 15.55.

N- $\beta$ -Chloroethyl-N'-*p*-anisylurea was identified further by cyclization to the known 1-*p*-anisyl-2-imidazolidone.<sup>6</sup> N- $\beta$ -Chloroethyl-N'-*p*-anisylurea (32.7 mg., 0.00014 mole) was heated in a solution of 1.58 mg. (0.00028 mole) of potassium hydroxide in 2 cc. of 95% ethanol for 10 minutes. On cooling 16.3 mg. (59.5%) of crystals, which melted at 213–213.5°, was obtained. A mixed melting point determination with an authentic sample of 1-*p*-anisyl-2-imidazolidone was not depressed.

The alkaline filtrate from the crude N- $\beta$ -chloroethyl-N'-*p*-anisylurea was acidified to a pH 1 with 10% hydrochloric acid solution. A white precipitate (m.p. 136°) formed immediately; yield 1.725 g. (46.3%). After one crystallization from 95% methanol, the product melted at 146.5° alone and on admixture with an authentic sample of N- $\beta$ -nitraminoethyl-N'-*p*-anisylurea.<sup>7</sup>

**N- $\beta$ -Chloroethyl-N'-*p*-anisylurea.**—A benzene solution of  $\beta$ -chloroethylamine was prepared by adding 10 g. (0.86 mole) of  $\beta$ -chloroethylamine hydrochloride<sup>11</sup> to aqueous alkali covered with benzene as previously described.<sup>7</sup> To the dried benzene solution 9.64 g. (0.064 mole) of *p*-anisyl isocyanate was added. After addition of 70 cc. of petroleum ether (b.p. 30–60°), the solid was removed by filtration; yield 14.38 g. (98.2%). The melting point was raised from 158 to 161° by crystallizing from 95% alcohol. The melting point was not depressed on admixture with the N- $\beta$ -chloroethyl-N'-*p*-anisylurea obtained from the reaction of acetyl chloride with N- $\beta$ -nitraminoethyl-N'-*p*-anisyl-N"-nitroguanidine.

Three grams (0.013 mole) of N- $\beta$ -chloroethyl-N'-*p*-anisylurea refluxed for five minutes with 1.47 g. (0.026 mole) of potassium hydroxide in 15 cc. of 70% ethanol gave 2.20 g. (88.0%) of 1-*p*-anisyl-2-imidazolidone.<sup>6</sup> One crystallization from 95% ethanol (45.4 cc./g.) raised the melting point from 209.5 to 213.5°.

**Effect of Acetyl Chloride on 1-Nitro-2-*p*-acetamidophenylamino-2-imidazoline.**—To 800 mg. (0.003 mole) of 1-nitro-2-*p*-acetamidophenylamino-2-imidazoline was added 0.715 g. (0.009 mole) of acetyl chloride, 0.913 g. (0.009 mole) of acetic anhydride and 10 cc. of glacial acetic acid. This mixture was heated with stirring at 41° for one hour. On

(7) A. F. McKay, *J. Org. Chem.*, **16**, 1395 (1951).

(8) All melting points are uncorrected.

(9) Microanalyses were performed by C. W. Beazley, Skokie, Illinois.

(10) A. P. N. Franchimont, *Rec. trav. chim.*, **16**, 213 (1897).

(11) K. Ward, Jr., *This Journal*, **57**, 914 (1935).

removal of the volatile solvents a residue of 1-nitro-2-*p*-acetamidophenylamino-2-imidazolium chloride remained; yield 842 mg. (92.4%). This compound melted with decomposition at 189° and gave a deep green color in the Franchimont test using dimethylaniline. It gave a positive test for chlorine with aqueous silver nitrate solution. An aliquot was converted into the picrate (m.p. 178° with decomposition) in the usual manner.

*Anal.* Calcd. for  $C_{17}H_{16}N_8O_{10}$ : C, 41.38; H, 3.45; N, 22.72. Found: C, 41.61; H, 3.44; N, 22.46.

A portion of 500 mg. (0.00167 mole) of the 1-nitro-2-*p*-

acetamidophenylamino-2-imidazolium hydrochloride was dissolved in 10 cc. of cold 10% sodium hydroxide solution. After it had remained at room temperature for 15 minutes, it was acidified to pH 1 with 10% aqueous hydrochloric acid solution. The crude product (m.p. 194° with decomposition) was removed by filtration and washed with water; yield 382 mg. (81.3%). One crystallization from ethanol raised the melting point to 204° with decomposition and it did not depress the melting point of an authentic sample of *N*- $\beta$ -nitraminoethyl-*N'*-*p*-acetamidophenylurea<sup>4</sup> on admixture.

OTTAWA, CANADA

[CONTRIBUTION FROM THE CHEMICAL RESEARCH DIVISION OF SCHERING CORPORATION]

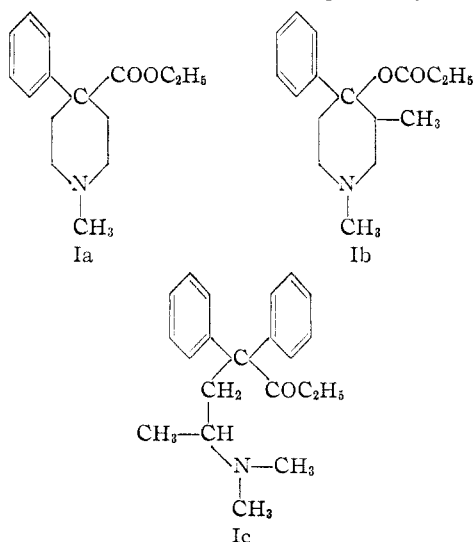
## Synthesis of 4,4-Diphenyl-1-methylpiperidine<sup>1</sup>

BY NATHAN SPERBER, MARGARET SHERLOCK AND DOMENICK PAPA

RECEIVED OCTOBER 13, 1952

4,4-Diphenyl-1-methylpiperidine has been synthesized by several procedures based on the dialkylation of diphenylmethane with substituted  $\beta$ -ethyl halides. Subsequent cyclization of the dialkylated products to the piperidine ring system was studied.

In recent years, a number of structures representing various fragments of the morphine molecule have been synthesized and tested for analgesic activity.<sup>2</sup> Among these structural types, several compounds derived from 4-phenyl-1-methylpiperidine; *i.e.*, ethyl 4-phenyl-1-methylpiperidine-4-carboxylate (Ia)<sup>3</sup> and *dl*-1,3-dimethyl-4-phenyl-4-propionoxypiperidine (Ib),<sup>4</sup> possess high analgesic activity and are in clinical use under the trade names Demerol and Nisentil, respectively. In our



investigations on analgesic agents, 4,4-diphenyl-1-methylpiperidine (VI) was synthesized to determine whether the introduction of a second phenyl group into the 4-phenyl-1-methylpiperidine moiety

would yield a compound with pronounced analgesic activity.<sup>5</sup> In this respect VI has in common with Amidone (Ic)<sup>6</sup> a *gem*-diphenyl group and may be considered a hybrid structure of types Ia and Ic. Structurally, VI is also closely related to the recently described 1-methyl-4,4-diphenyl-3-piperidone, a cyclic analog of Amidone.<sup>7</sup>

The simplest approach to VI appeared to be the alkylation of diphenylmethane with *N,N*-bis-( $\beta$ -chloroethyl)-benzylamine<sup>8</sup> with the formation of 4,4-diphenyl-1-benzylpiperidine. However, this reaction gave only the linear product *N,N*-bis-(3,3-diphenylpropyl)-benzylamine. Several closely related synthetic routes were then studied which depended upon the dialkylation of diphenylmethane with ethyl halides possessing functional groups in the  $\beta$ -position followed by cyclization of the dialkylated products.

Diphenylmethylpotassium<sup>9</sup> was treated with  $\beta$ -bromoethyl ethyl ether in liquid ammonia to give 3,3-diphenyl-1-ethoxypropane (II). Alkylation of II with  $\beta$ -dimethylaminoethyl chloride yielded 5-ethoxy-3,3-diphenyl-*N,N*-dimethylamylamine (III) and cleavage of the ethoxy group gave the corresponding carbinol IV. The reaction of IV with thionyl chloride gave 4,4-diphenyl-1,1-dimethylpiperidinium chloride (V), which on sublimation *in vacuo* yielded 4,4-diphenyl-1-methylpiperidine (VI).<sup>10</sup>

(5) Shortly before this work was completed, L. O. Randall and G. Lehmann, *J. Pharmacol. Exp. Therap.*, **93**, 314 (1948), evaluated VI, along with several other series of compounds, and found it to be devoid of analgesic activity. However, no reference to the chemistry of the compound was given.

(6) M. Bockmühl and G. Ehrhart, *Ann.*, **561**, 52 (1949).

(7) F. F. Blicke and J. Krapcho, *THIS JOURNAL*, **74**, 4001 (1952).

(8) This approach was based on the procedure of O. Eisleb (*Ber.*, **74**, 1433 (1941)), who prepared 1-methyl-4,4-diphenylpiperidine in good yield by the alkylation of fluorene with bis-( $\beta$ -chloroethyl)-methylamine and sodamide.

(9) R. S. Yost and C. R. Hauser, *THIS JOURNAL*, **69**, 2325 (1947).

(10) This reaction is based on the method of O. Hieronimus, Dissertation, Berlin, 1938, as described in the chapter by F. F. Blicke, "Organic Reactions," Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1942, p. 324. A similar type of cyclization to a piperidinium salt, followed by the removal of methyl bromide to yield the corresponding substituted piperidine, has been described by K. Miescher and H. Kaegi, U. S. Patents 2,486,792-2,486,796 (1949).

(1) Presented in Abstract before the Division of Medicinal Chemistry at the 122nd Meeting of the American Chemical Society, Atlantic City, N. J., September, 1952.

(2) For a discussion of this subject, see J. Lee, A. Ziering, L. Berger and S. D. Heineman, in "Jubilee Volume Emil Barends," Reinhardt, Basel, 1946, p. 264; L. Small, *Ann. N. Y. Acad. Sci.*, **51**, 12 (1948); F. Bergel and A. L. Morrison, *Quart. Rev. Chem. Soc.*, **2**, 349 (1948); J. Lee, in "Medicinal Chemistry," Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1951, p. 438.

(3) O. Eisleb and O. Schaumann, *Deut. med. Wochschr.*, **65**, 967 (1939).

(4) A. Ziering and J. Lee, *J. Org. Chem.*, **12**, 911 (1947).