SYNTHESIS OF N'-SUBSTITUTED 4-AMINOPIPERIDINES WITH A SHIELDED NITROGEN ATOM

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A method was developed for the synthesis of N-substituted 2,2,6,6-tetramethyl- and 1,2,-2,6,6-pentamethyl-4-aminopiperidines starting from triacetoneamine cyanohydrin through the corresponding aminonitriles with subsequent reductive decyanation. The peculiarities of salt formation from N-substituted 4-aminopiperidines with a shielded nitrogen atom are examined.

N'-Substituted 4-aminopiperidines are of considerable interest as analgesics (fentanyl), neuroleptics (propipfon, droperidol, and piperonyl), and antihistamines (thenaldine). In addition, in a series of piperidine derivatives that do not contain an amino group in the 4 position, it was shown that shielding of the cyclic nitrogen by the introduction of four α-methyl groups leads to an increase in the activity of the compounds (as in the medicinal preparations pyrilene and eucaine A). In this connection, it seemed of interest to synthesize N'-substituted 4-aminopiperidines with a shielded nitrogen atom, four methyl groups in the 2 and 6 positions of the piperidine ring, and five methyl groups in the 1, 2, and 6 positions. Only the synthesis of 1,2,2,6,6-pentamethyl-4-aminopiperidine and its guanidine derivative [1] and the reaction of triacetoneamine cyanohydrin with piperidine and morpholine with subsequent converstion of the resulting 2,2,6,6-tetramethyl-4-cyano-4-morpholino(or piperidino)piperidines, under the influence of organomagnesium compounds, to 2,2,6,6-tetramethyl-4-alkyl-4-morpholino(or piperidino)piperidines [2] are described in the literature.

We have made a detailed study of the reaction of triacetone cyanohydrin (I) with ammonia and various amines. It was shown that I in methanol at 0 to 20°C readily reacts with aliphatic and aliphatic-aromatic amines and ammonia to form the corresponding 2,2,6,6-tetramethyl-4-cyano-4-aminopiperidines (II). Aromatic amines (aniline, for example), which are weaker bases, do not undergo this reaction. α-Aminonitriles II, which are generated as a result of the reaction of triacetoneamine cyanohydrin with amines, are thermally unstable and, on heating above 50°, readily split out hydrogen cyanide to form tetramethylpiperidines III and IV.

We have previously noted [3] that the double bond in unsaturated 4-substituted 2,2,6,6-tetramethylpiperidines is usually in the 3,4 position of the piperidine ring. The energic advantageousness of Δ^3-dehydropiperidines is so high that, in the case of unsaturated 4-alkoxycarbonylmethyl derivatives, the double bond even withdraws from conjugation in order to occupy the 3,4 endocyclic position.

It was demonstrated by means of PMR spectroscopy (the absence of a signal from a vinyl proton in the 3 position of the piperidine ring) that the double bond in analogous unsaturated N'-substituted 4-aminotetramethylpiperidines (III) remains exocyclic and characteristic for imines, and derivatives of enamines with an endocyclic Δ^3-dehydropiperidine double bond are formed only in the case of tertiary amines IV.

It should be noted that the synthesis (described in this paper) of 2,2,6,6-tetramethyl-4-imino derivatives of piperidine (III) from triacetoneamine through its cyanohydrin (I) and aminonitriles (II) with subse-

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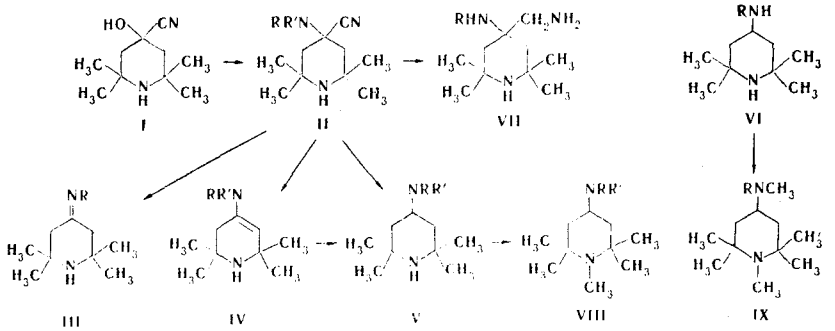
TABLE 1. PMR Spectra of N'-Substituted 4-Aminopiperidines and Their Methiodides*

Compound		Chemical shifts, δ, ppm					Solvent
		1-CH_3	2- and 6-$(CH_3)_2$	4-H	α-CH_2 (and (CH_3) rel. to 4-N	N^+—CH_3	
VIII $NRR'=N(CH_2)_4$	Base	2,26	1,07 1,17	2,61	2,61		CD_3OD
	Methiodide	2,28	1,16 1,27	3,80	3,68	2,92	
VIII $NRR'=N(CH_2)_5$	Base	2,25	1,06 1,18	2,70	2,55		CD_3OD
	Methiodide	2,32	1,19 1,30	3,88	3,55	3,01	
IX $R=CH_2C_6H_5$	Base	2,13	0,94 1,12	2,74	CH_3 2,18 CH_2 3,52		CCl_4
	Methiodide	2,28	1,32 1,18	4,09	CH_3 3,04 CH_2 4,78	3,04	

*The PMR spectra were recorded with a JNM-4H-100 spectrometer with tetramethylsilane as the internal standard.

quent dehydrocyanation of them proceeds under mild conditions and gives considerably higher yields of imines III of better quality than in the direct reaction of triacetoneamine with primary amines.



The decyanation of aminonitriles II proceeds readily not only as a result of splitting out of hydrogen cyanide but also by reduction of these compounds with lithium aluminum hydride. The normal reduction of the nitrile group and the formation of triamines of the VII type in yields of 42 and 75%, respectively, was observed only in the case of the 4-amino (II, $R=R_1=H$) and 4-benzylamino derivatives (II, $R=C_6H_5CH_2$, $R'=H$). In all of the remaining α-aminonitriles (II), the cyano group was eliminated on reaction with lithium aluminium hydride, and the pure N'-substituted 2,2,6,6-tetramethyl-4-aminopiperidines (V) were obtained in 80-85% yields. The indicated reactions can be considered to be a convenient preparative method for compounds of the V type. Another synthetic route, which is usually employed for the conversion of 4-oxopiperidines to N'-substituted 4-amino derivatives – the reaction of the oxo derivative with amines and subsequent reduction of the imines with complex metal hydrides or catalytically – does not give satisfactory results in the case of triacetoneamine. Because of the instability of the 2,2,6,6-tetramethyl-4-iminopiperidines, which are usually altered during the synthesis with opening of the piperidine ring and resinification, the yields of VI via this scheme are low, and the compounds are contaminated with hard-to-separate side products. N',N'-Disubstituted 4-amino-2,2,6,6-tetramethylpiperidines cannot be obtained at all via the direct reaction of triacetoneamine with secondary amines.

N'-Substituted 2,2,6,6-tetramethyl-4-aminopiperidines V and VI are readily methylated at the piperidine nitrogen atom under the influence of formic acid and formalin. If the exocyclic nitrogen atom in the 4 position is secondary, it is also simultaneously methylated. The resulting N',N'-disubstituted 1,2,2,6,6-pentamethyl-4-aminopiperidines are strong diacidic bases that give stable dihydrochlorides. In addition, because of steric hindrance, these bases form only monoquaternary salts with methyl iodide. Proof of the quaternization at the exocyclic rather than the endocyclic nitrogen atom during the formation of these monoquaternary salts was obtained by means of the PMR spectra.

TABLE 2. N'-Substituted 2,2,6,6-Tetramethyl-4-cyano-4-aminopiperidines (II)

NRR'	mp, °C	Empirical formula	Found, %				Calc., %				Yield, %
			C	H	N	Cl	C	H	N	Cl	
$N(CH_2)_5$	90—92	$C_{15}H_{27}N_3$	72,1	10,8	16,7	—	72,2	10,9	16,9	—	73
	173—175	$C_{15}H_{27}N_3 \cdot 2HCl$	—	—	12,7	21,7	—	—	13,0	22,0	—
$O(CH_2CH_2)_2N$	106—108	$C_{14}H_{25}N_3O$	66,4	9,8	17,1	—	66,9	10,0	16,7	—	81
	162—164	$C_{14}H_{25}N_3O \cdot 2HCl$	—	—	13,1	22,2	—	—	13,0	21,9	—
$N(CH_2)_4$	74—76	$C_{14}H_{25}N_3$	71,6	10,4	17,9	—	71,4	10,7	17,9	—	70
	152—154	$C_{14}H_{25}N_3 \cdot 2HCl \cdot 2H_2O$	—	—	12,2	20,6	—	—	12,2	20,6	—
$C_6H_5CH_2NH$	66—68	$C_{17}H_{25}N_3$	75,6	9,2	15,9	—	75,2	9,3	15,5	—	67
	80*	$C_{17}H_{25}N_3 \cdot 2HCl \cdot 2H_2O$	—	—	10,9	18,4	—	—	11,0	18,6	—
$CH_3(CH_2)_3NH$	49—51	$C_{14}H_{27}N_3$	70,8	11,3	17,8	—	70,9	11,5	17,7	—	56
	85*	$C_{14}H_{27}N_3 \cdot 2HCl \cdot 2H_2O$	—	—	12,1	20,2	—	—	12,1	20,5	—
$(CH_3)_2N$†	35—37	$C_{12}H_{23}N_3$	68,5	11,0	19,7	—	68,8	11,1	20,1	—	83
NH_2†	75—78	$C_{10}H_{19}N_3$	65,9	10,5	23,1	—	66,2	10,6	23,2	—	77

*With decomposition.

†The reaction was carried out by saturating the reaction mass with ammonia or amine at 0° and allowing it to stand at 0° for 10 days.

From a comparison of the spectra of the bases and methiodides of VIII [NRR' = $N(CH_2)_4$ and $N(CH_2)_5$] and IX (R = $CH_2C_6H_5$) (see Table 1), it is apparent that the greatest changes in the chemical shifts that characterize quaternization of the adjacent nitrogen atom are observed for the signals of the protons in the 4 position of 1,2,2,6,6-pentamethylpiperidine ring and the signals of the protons in the adjacent groupings.

In the spectra of the methiodides of VIII [NRR' = $N(CH_2)_4$ and $N(CH_2)_5$], the signals of the methylene protons of the pyrrolidine and piperidine rings in the α positions relative to 4-N are shifted by 1.00-1.07 ppm to weaker field as compared with the signals of these protons in the free bases, and for IX (R = $CH_2C_6H_5$), the signals of the CH_3 and CH_2 groups in the α positions relative to 4-N in the spectrum of the methiodide are shifted by 0.86 and 1.26 ppm, respectively. The signals of the 4-H proton in all of the investigated compounds also experience weak-field shifts of 1.18-1.35 ppm on passing from the bases to the methiodides. At the same time, the shift of the proton signals on quaternization of the compounds is ~0.25-0.02 ppm for the groupings adjacent to 1-N (the N-methyl group and the methyl groups in the 2 and 6 positions of the piperidine ring). This sort of character of the change in the chemical shifts indicates that the exocyclic rather than the endocyclic nitrogen atom undergoes reaction with methyl iodide.

EXPERIMENTAL

2,2,6,6-Tetramethyl-4-cyano-4-pyrrolidinopiperidine [II, NRR' = $N(CH_2)_4$]. Pyrrolidine [5.8 g (83 mmole)] was added to a solution of 10 g (55 mmole) of triacetoneamine cyanohydrin (I) in 120 ml of methanol, and the mixture was allowed to stand at 17-20° for 10 days in a flask with a calcium chloride tube. The methanol was removed by vacuum distillation at a bath temperature no higher than 30-40°, and the residue was cooled. The resulting crystalline mass was squeezed on a porous funnel and washed on the filter with cold (-5°) petroleum ether to give 9.1 g (70%) of II [NRR' = $N(CH_2)_4$] as colorless crystals with mp 74-76°. The crystals were soluble in the usual organic solvents. The dihydrochloride was obtained as colorless crystals with mp 152-154°. The remaining N'-substituted 2,2,6,6-tetramethyl-4-cyano-4-aminopiperidines (Table 2) were similarly synthesized.

2,2,6,6-Tetramethyl-4-benzyliminopiperidine (III, R = $CH_2C_6H_5$). Benzylamine [4.6 g [43 mmole)] was added to a solution of 5 g (27 mmole) of I in

TABLE 3. N'-Substituted 2,2,6,6-Tetramethyl-4-aminopiperdines (V)

NRR'	bp, °C (mm)	n_D^{20}	Empirical formula	Found, %			Calc., %			Yield, %
				C	H	N	C	H	N	
$(CH_2)_5N$	99—101 (4)	1,4820	$C_{14}H_{28}N_2$	75,1	12,6	12,9	74,9	12,6	12,5	83
$O(CH_2CH_2)_2N$	*		$C_{13}H_{26}N_2O$	69,2	11,8	12,2	69,0	11,6	12,4	80
$(CH_2)_4N$	95—96 (4)	1,4790	$C_{13}H_{26}N_2$	74,3	12,3	13,6	74,2	12,4	13,3	80
$(CH_3)_2N$	59—60 (4)	1,4600	$C_{11}H_{24}N_2$	71,5	12,9	15,6	71,7	13,1	15,2	85

*mp 52-54°

60 ml of methanol, and the mixture was allowed to stand at 18-20° for 10 days in a flask with a calcium chloride tube. The methanol was removed by distillation, and the residue was dissolved in ether. The ether solution was dried with calcined magnesium sulfate, and the ether was removed by distillation. The residue was vacuum-distilled to give 3.75 g (56%) of imine III ($R=CH_2C_6H_5$) as a colorless liquid with bp 140-142° (1 mm) that was quite soluble in the usual organic solvents; n_D^{20} 1.5310. Found: C 78.7; H 9.8; N 11.7%. $C_{16}H_{24}N_2$. Calculated: C 78.6; H 9.9; N 11.5%.

2,2,6,6-Tetramethyl-4-n-butyliminopiperidine (III, $R=n-C_4H_9$). This compound was similarly obtained in 49% yield from 10 g (54 mmole) of cyanohydrin I and 6.64 g (91 mmole) of n-butylamine and had bp 92-94° (4 mm) and n_D^{20} 1.4700. Found: C 73.9; H 12.6; N 13.5%. $C_{13}H_{26}N_2$. Calculated: C 74.2; H 12.5; N 13.3%.

2,2,6,6-Tetramethyl-4-benzylaminopiperidine (VI, $R=CH_2C_6H_5$). A 6.5-g (26 mmole) sample of imine III ($R=CH_2C_6H_5$) in 100 ml of absolute alcohol was hydrogenated in the presence of 0.2 g of a platinum catalyst prepared by the Adams method to give 5.65 g (86%) of VI ($R=CH_2C_6H_5$) as a colorless liquid with bp 142-144° (4 mm). Found: C 77.9; H 10.7; N 11.4%. $C_{16}H_{26}N_2$. Calculated: C 78.0; H 10.6; N 11.4%.

2,2,6,6-Tetramethyl-4-n-butylaminopiperidine (VI, $R=n-C_4H_9$). A) A 2.75-g (13 mmole) sample of imine III ($R=n-C_4H_9$) in 50 ml of absolute alcohol was hydrogenated in the presence of 0.1 g of a platinum catalyst to give 2.3 g (83%) of VI ($R=n-C_4H_9$) as a colorless liquid with bp 90-92° (4 mm) and n_D^{20} 1.4613. Found: C 73.6; H 13.3; N 13.1%. $C_{13}H_{26}N_2$. Calculated: C 73.5; H 13.3; N 13.2%.

B) A 5.3-g (22 mmole) sample of 2,2,6,6-tetramethyl-4-cyano-4-n-butylaminopiperidine (II, R = H, $R'=n-C_4H_9$) in ether was reduced by means of 2.5 g (65 mmole) of lithium aluminum hydride to give 3.7 g (78%) of amine VI ($R=n-C_4H_9$) with bp 90-92° (4 mm) and n_D^{20} 1.4615.

2,2,6,6-Tetramethyl-4-dimethylamino-Δ^3-dehydropiperidine (IV, $R=R'=CH_3$). A total of 50 ml of a 10% solution of dimethylamine in methanol was added to a solution of 9 g (49 mmole) of I in 90 ml of methanol, and the mixture was allowed to stand at 18-20° for 10 days in a flask with a calcium chloride tube. The methanol was removed by distillation, and the residue was dissolved in ether. The ether solution was dried with calcined magnesium sulfate, and the ether was removed by distillation. The residue was vacuum-distilled to give 6.7 g (74%) of dehydropiperidine IV ($R=R'=CH_3$) as a colorless liquid with bp 88-90° (7 mm). Found: C 72.6; H 11.8; N 15.5%. $C_{11}H_{22}N_2$. Calculated: C 72.5; H 12.2; N 15.4%.

2,2,6,6-Tetramethyl-4-pyrrolidine-Δ^3-dehydropiperidine [IV, $NRR'=N(CH_2)_4$]. A mixture of 5 g (27 mmole) of I, 10 ml of pyrrolidine, and 30 ml of benzene was heated for 5 h in a Dean-Stark apparatus. Water liberation was complete after this heating period. The benzene was removed from the reaction mass by distillation, and the residue was vacuum-distilled to give 5.6 g of a mixture of liquid and solid with bp 100-120° (1 mm). The mixture was allowed to stand overnight at -5 to 0° to give 1.1 g (17%) of a precipitate that was identified as II [$NRR'=N(CH_2)_4$]. The filtrate was vacuum-distilled to give 3 g (53%) of dehydropiperidine IV [$NRR'=N(CH_2)_4$] as a colorless liquid with bp 97-100° (1 mm) and n_D^{20} 1.5010. Found: C 75.0; H 11.6; N 13.6%. $C_{13}H_{24}N_2$. Calculated: C 74.9; H 11.6; N 13.5%.

2,2,6,6-Tetramethyl-4-morpholino-Δ^3-dehydropiperidine [IV, $NRR'=O(CH_2CH_2)N$]. This compound was similarly obtained from 5 g (27 mmole) of I, 10 ml of morpholine, and 30 ml of benzene. After removal of the benzene by distillation, the residue was vacuum-distilled at 1 mm to give 3.4 g (80%) of a fraction (I) with bp 60-63° and mp 34-36°, which was identified as triacetoneamine, and 1.5 g of a fraction (II) that boiled

TABLE 4. N'-Substituted 1,2,2,6,6-Pentamethyl-4-aminopiperidines (VIII)

NRR'	bp, °C (mm) or mp	Empirical formula	Found, %					Calc., %					Yield, %
			C	H	N	Cl	I	C	H	N	Cl	I	
$(CH_2)_5N$	119—120 (5)	$C_{15}H_{30}N_2$	75,8	12,6	11,8	—	—	75,7	12,7	11,8	—	—	86
	269—271	$C_{15}H_{30}N_2 \cdot 2HCl \cdot H_2O$	—	—	8,7	21,6	—	—	—	8,5	21,5	—	—
	258—260	$C_{16}H_{33}IN_2$	—	—	7,4	—	33,2	—	—	7,4	—	33,4	—
$O(CH_2CH_2)_2N$	80—82	$C_{14}H_{28}N_2O$	70,0	11,9	11,6	—	—	69,9	11,7	11,6	—	—	76
	278—280	$C_{14}H_{28}N_2O \cdot 2HCl \cdot H_2O$	—	—	8,3	21,4	—	—	—	8,5	21,4	—	—
	228—230	$C_{15}H_{31}IN_2O$	—	—	7,7	—	33,2	—	—	7,3	—	33,2	—
$(CH_2)_4N$	108—110 (3)	$C_{14}H_{28}N_2$	75,2	12,5	12,4	—	—	74,9	12,6	12,5	—	—	80
	283—285	$C_{14}H_{28}N_2 \cdot 2HCl \cdot H_2O$	—	—	8,9	22,5	—	—	—	8,9	22,5	—	—
	248—250	$C_{15}H_{31}IN_2$	—	—	7,5	—	34,2	—	—	7,3	—	34,6	—
$(CH_3)_2N$	30—32	$C_{12}H_{26}N_2$	72,7	13,0	14,0	—	—	72,7	13,2	14,1	—	—	75
	265—267	$C_{12}H_{26}N_2 \cdot 2HCl$	—	—	10,2	26,1	—	—	—	10,3	26,1	—	—
	253—257	$C_{13}H_{29}IN_2$	—	—	8,1	—	37,8	—	—	8,2	—	37,3	—

up to 135°. Fraction II was redistilled to give 0.75 g (12%) of a compound with bp 117-120° (1 mm), which was identified as IV [NRR' = $O(CH_2CH_2)N$]. Found: C 69.0; H 10.5; N 12.1%. $C_{13}H_{24}N_2O$. Calculated: C 69.9; H 10.8; N 12.5%.

2,2,6,6-Tetramethyl-4-piperidinopiperidine [V, NRR' = $N(CH_2)_5$]. A 5-g (20 mmole) sample of cyanoamine II [NRR' = $N(CH_2)_5$] in ether was reduced by means of 1.6 g (40 mmole) of lithium aluminum hydride to give 3.7 g (82%) of diamine V [NRR' = $N(CH_2)_5$] as a colorless liquid with bp 99-101° (4 mm) and n_D^{20} 1.4820. Found: C 75.1; H 12.6; N 12.9%. $C_{14}H_{28}N_2$. Calculated: C 74.9; H 12.6; N 12.5%.

The other diamines (V) were similarly synthesized (Table 3).

2,2,6,6-Tetramethyl-4-dimethylaminopiperidine (V, R = R' = CH_3). A 3.7-g (20 mmole) sample of dehydropiperidine IV (R = R' = CH_3) was reduced with hydrogen in absolute alcohol in the presence of 0.4 g of a platinum catalyst to give 1.55 g (41%) of diamine V (R = R' = CH_3) as a colorless liquid with bp 59-60° (4 mm) and n_D^{20} 1.4600. Found: C 72.0; H 12.9; N 15.1%. $C_{11}H_{24}N_2$. Calculated: C 71.7; H 13.1; N 15.2%.

2,2,6,6-Tetramethyl-4-benzylamino-4-aminomethylpiperidine (VII, R = $CH_2C_6H_5$). A 2.5-g (9 mmole) sample of cyanoamine II (R = H, R' = $CH_2C_6H_5$) was reduced by means of 1.4 g (36 mmole) of lithium aluminum hydride in ether–benzene to give 1.9 g (75%) of triamine VII (R = $CH_2C_6H_5$) as colorless crystals with mp 83.85°. Found: C 74.1; H 10.6; N 15.3%. $C_{17}H_{29}N_3$. Calculated: C 74.1; H 10.6; N 15.3%. The trihydrochloride was obtained as colorless crystals with mp 215-217° (dec.). Found: Cl 25.3; N 10.3%. $C_{17}H_{29}N_3 \cdot 3HCl \cdot 2H_2O$. Calculated: Cl 25.3; N 10.0%.

2,2,6,6-Tetramethyl-4-amino-4-aminomethylpiperidine (VII, R = H). A 3-g (16 mmole) sample of cyanoamine II (R = R' = H) was reduced by means of 2.5 g (66 mmole) of lithium aluminum hydride in ether–benzene to give 1.3 g (42%) of triamine VII (R = H) as a colorless liquid with bp 122-123° (15 mm) and n_D^{20} 1.4898. Found: C 64.9; H 12.7; N 22.2%. $C_{10}H_{23}N_3$. Calculated: C 64.8; H 12.5; N 22.7%. The trihydrochloride was obtained as colorless crystals with mp 256-258° (dec.). Found: Cl 32.0; N 13.0%. $C_{10}H_{23}N_3 \cdot 3HCl \cdot 2H_2O$. Calculated: Cl 32.2; N 12.7%.

1,2,2,6,6-Pentamethyl-4-piperidinopiperidine [VIII, NRR' = $N(CH_2)_5$]. A mixture of 3.35 g (15 mmole) of diamine V [NRR' = $N(CH_2)_5$], 2.06 g (45 mmole) of formic acid, 1.43 g of 35% formalin (16.5 mmole), and 2.24 ml of water was heated for 15 h on a boiling-water bath. The reaction mass was cooled, made alkaline with excess 50% potassium carbonate solution, and extracted with ether. The extract was dried with potassium carbonate, and the ether was removed by distillation. The residue was vacuum-distilled to give 3.05 g (86%) of VIII [NRR' = $N(CH_2)_5$] as a colorless liquid with bp 119-120° (5 mm) and n_D^{20} 1.4920. The dihydrochloride was obtained as colorless crystals with mp 269-271° (dec.). The monomethiodide was obtained as colorless crystals with mp 258-260°.

The other N'-substituted 1,2,2,6,6-pentamethyl-4-aminopiperidines (VIII) and their hydrochlorides and monomethiodides were similarly obtained (Table 4).

1,2,2,6,6-Pentamethyl-4-(N-benzyl-N-methylamino)piperidine (IX, R = $CH_2C_6H_5$). A mixture of 4.9 g (20 mmole) of VI (R = $CH_2C_6H_5$), 5.5 g (120 mmole) of formic acid, 3.8 g of 35% formalin (44 mmole) and 3.3 g of water was heated on a boiling-water bath for 15 h. The reaction mixture was then worked up as described for VIII to give 4.15 g (76%) of IX (R = $CH_2C_6H_5$) as a colorless liquid with bp 145-147° (2 mm) and n_D^{20} 1.5160. Found: C 78.7; N 11.2; N 9.9%. $C_{18}H_{30}N_2$. Calculated: C 78.8; H 11.0; N 10.2%. The dihydrochloride was obtained as colorless crystals with mp 85° (dec.). Found: Cl 19.0; N 7.0%. $C_{18}H_{30}N_2 \cdot 2HCl \cdot 2H_2O$. Calculated: Cl 18.5; N 7.3%. The monomethiodide was obtained as colorless crystals with mp 225-227°. Found: I 30.1; N 6.9%. $C_{19}H_{33}IN_2$. Calculated: I 30.5; N 6.7%.

1,2,2,6,6-Pentamethyl-4-(N-n-butyl-N-methylamino)piperidine (IX, R = n-C_4H_9). A mixture of 4.82 g (23 mmole) of VI (R = n-C_4H_9), 6.27 g (140 mmole) of formic acid, 4.3 g of 35% formalin (49 mmole), and 3.2 ml of water was treated as described above for IX (R = $CH_2C_6H_5$) to give 4.05 g (74%) of IX (R = n-C_4H_9) as a colorless liquid with bp 103-106° (4 mm) and n_D^{20} 1.4690. Found: C 74.9; N 13.2; N 11.7%. $C_{15}H_{32}N_2$. Calculated: C 74.9; H 13.4; N 11.7%. The dihydrochloride was a colorless crystalline substance with mp 251-253°. Found: Cl 22.3; N 8.9%. $C_{15}H_{32}N_2 \cdot 2HCl$. Calculated: Cl 22.6; N 8.9%. The monomethiodide was obtained as colorless crystals with mp 180-182°. Found: I 33.4; N 7.3%. $C_{16}H_{35}IN_2$. Calculated: I 33.2; N 7.3%.

LITERATURE CITED

1. W. Lutz, S. Lazarus, and R. Meltzer, J. Org. Chem., 27, 1695 (1962).
2. V. A. Zagorevskii and K. I. Lopatina, Zh. Organ. Khim., 1, 1500 (1965).
3. E. S. Nikitskaya, E. S. Levkoeva, V. S. Usovskaya, L. N. Yakhontov, and M. V. Rubtsov, Khim. Geterotsikl. Soedin., 230 (1971).