

4-Substituted Piperidines. III. Reduction of 1-Benzyl-4-cyano-4-*t*-aminopiperidines with Lithium Aluminium Hydride

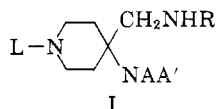
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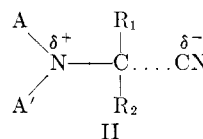
The reduction of 1-benzyl-4-cyano-4-*t*-aminopiperidines with lithium aluminium hydride is described; this reduction results in denitrilation, whereas the same reduction of the corresponding primary carboxamides yields the expected primary amines, which can easily be acylated. The obtained compounds are debenzylated, after which other substituents are introduced. These new compounds are virtually devoid of hypotensive or CNS-depressant activity.

In the previous papers of this series the synthesis¹ of 1-benzyl-4-cyano-4-*t*-aminopiperidines and subsequent reactions (hydrolysis¹ and organometal reactions²) were discussed. The purpose of this paper is to describe reductive reactions on the same starting α -aminonitriles and the acylation of the thus-formed primary amines to obtain compounds of another type of 4,4-disubstituted piperidines, namely products of the general formula I, in which NAA' stands for a dialkyl-amino group or a saturated heterocyclic moiety; R

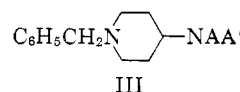


stands for H, COalk, or COOalk; and L represents any substituent retaining the basic character of the piperidine ring system.

As already indicated in the previous papers, α -aminonitriles have specific properties. So it is known from the literature that the reduction of the nitrile group of these compounds very often takes an abnormal course. Reduction to the primary amines with hydrogen, prepared by dissolution of metallic sodium in alcohol, usually gives rather low yields of the expected reaction products,^{3,4} whereas in one case the formation of denitrilated amine was reported.⁵ On the other hand, fair-to-good yields are mentioned for catalytic reduction reactions and this method seems to be better than the sodium-alcohol method.⁶ As far as the compounds described in this paper are concerned, difficulties may be expected as simultaneous debenzylation will very probably occur. Welvert^{3,7} studied the reaction of a large number of α -aminonitriles with lithium aluminium hydride and found that, dependent on the nature of the nitrile, either normal reduction to the primary amine took place or the nitrile group was split off with formation of the corresponding amine. As in the case of reaction with organometallic compounds, this anomaly was explained by Welvert by assuming that the α -aminonitriles react in the form of an immonium ion II.



In the present compounds, the occurrence of this ion and the consequent formation of denitrilated compounds should be promoted by the presence of a quaternary carbon atom, and in fact, the corresponding denitrilated compounds III were isolated in high yields as sole reaction products from the reaction of 1-benzyl-4-cyano-4-*t*-aminopiperidines with LiAlH₄. In one instance (2), a conclusive proof of the structure of this 4-*t*-aminopiperidine was given by the unequivocal synthesis of this compound by the hydrogenation of the corresponding enamine, obtained from 1-benzyl-4-piperidone and pyrrolidine. Finally we succeeded in



preparing the desired primary amines in good yields by the reduction with LiAlH₄ of the primary carboxamides, obtained from the nitriles by hydrolysis.¹ Independent of our work, this same method was also successfully used by Schipper.⁸ These primary amines could then be treated in the usual manner with acyl halides or anhydrides and with chloroformate. The resulting carboxamides or urethans are listed in Table I, whereas the denitrilated benzylpiperidines are summarized in Table II. In the Experimental Section each of the reactions discussed above is illustrated by one example.

On hydrogenolysis of the benzyl group, all the above-mentioned compounds could be converted into the corresponding secondary nor compounds, which are listed in Tables I and II, and one example of this catalytic debenzylation is given in the Experimental Section. Finally, a number of different substituents were introduced on the piperidine ring system by the reaction of the secondary amines with halides. A representative choice of these condensation products is given in Tables III and IV.

Pharmacology.—The compounds described in this paper and also in the previous papers^{1,2} may be considered as being related to pethidine; the main difference consists in the replacement of 4-phenyl by a dialkylamino or a cyclic alkylenimino group. In the

(1) C. van de Westeringh, P. Van Daele, B. Hermans, C. Van der Eycken, J. Boey, and P. A. J. Janssen, *J. Med. Chem.*, **7**, 619 (1964).

(2) B. Hermans, P. Van Daele, C. van de Westeringh, C. Van der Eycken, J. Boey, and P. A. J. Janssen, *ibid.*, **8**, 851 (1965).

(3) Z. Welvert, *Compt. rend.*, **233**, 1121 (1951).

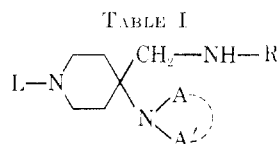
(4) M. S. Bloom, D. S. Breslow, and C. R. Hauser, *J. Am. Chem. Soc.*, **67**, 539 (1945).

(5) W. McMeeking and T. S. Stevens, *J. Chem. Soc.*, 347 (1933).

(6) (a) J. Corse, J. T. Bryant, and H. A. Shonle, *J. Am. Chem. Soc.*, **68**, 1905 (1946); (b) W. L. Hawkins and B. S. Biggs, *ibid.*, **71**, 2530 (1949).

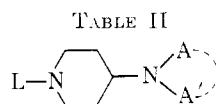
(7) Z. Welvert, *Compt. rend.*, **238**, 2536 (1954).

(8) E. Schipper and E. Chinery, *J. Org. Chem.*, **26**, 3597 (1961)



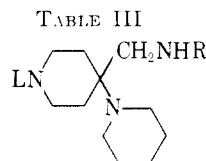
| Compd. | L | | R | Yield, % | B.p. (mm.) or m.p., °C. | Formula | Calcd., % | | | Found, % | | |
|--------|---|---|----------------------------------|----------|-------------------------|---|-----------------|-------|--------------|-----------------|-------|--------------|
| | | | | | | | Cl ⁻ | N | Neut. equiv. | Cl ⁻ | N | Neut. equiv. |
| 7 | C ₆ H ₅ CH ₂ | N(CH ₃) ₂ | H | 63 | 142–150 (0.05) | C ₁₅ H ₂₃ N ₃ | ... | 16.98 | 82 | ... | 16.73 | 85 |
| 8 | C ₆ H ₅ CH ₂ | N(CH ₃) ₂ | COCH ₃ | 27 | 98–100 | C ₁₇ H ₂₇ N ₃ O | ... | 14.52 | 145 | ... | 14.27 | 148 |
| 9 | C ₆ H ₅ CH ₂ | C ₆ H ₁₀ N ^a | H | 72 | 165 (0.5) | C ₁₈ H ₂₉ N ₃ | ... | 14.62 | 96 | ... | 14.91 | 93 |
| 10 | C ₆ H ₅ CH ₂ | C ₆ H ₁₀ N | COCH ₃ | 38 | 82–85 | C ₂₀ H ₃₁ N ₃ O | ... | 12.76 | 165 | ... | 12.61 | 168 |
| 11 | C ₆ H ₅ CH ₂ | C ₆ H ₁₀ N | COOC ₂ H ₅ | 45 | 235–237 | C ₂₁ H ₃₃ N ₃ O ₂ ·2HCl | 16.40 | 9.71 | 216 | 16.16 | 9.53 | 213 |
| 12 | C ₆ H ₅ CH ₂ | C ₄ H ₉ NO ^b | H | 72 | Oil ^c | C ₁₇ H ₂₇ N ₃ O | ... | ... | 96 | ... | ... | 101 |
| 13 | C ₆ H ₅ CH ₂ | C ₄ H ₉ NO | COCH ₃ | 48 | 243–245 | C ₁₉ H ₂₉ N ₃ O ₂ ·2HCl·H ₂ O ^d | 16.79 | 9.94 | 211 | 16.54 | 9.68 | 222 |
| 14 | H | C ₆ H ₁₀ N | COCH ₃ | 53 | 71–74 | C ₁₃ H ₁₆ N ₃ O | ... | 17.56 | 120 | ... | 17.24 | 122 |
| 15 | H | C ₆ H ₁₀ N | COOC ₂ H ₅ | 52 | 195–200 | C ₁₄ H ₂₇ N ₃ O ₂ ·2HCl | 20.72 | 12.28 | 171 | 20.29 | 12.01 | 174 |
| 16 | H | C ₄ H ₉ NO | COCH ₃ | 52 | 136–138.5 | C ₁₂ H ₂₃ N ₃ O ₂ | ... | 17.42 | 121 | ... | 17.23 | 122 |

^a Piperidino. ^b Morpholino. ^c Used without further purification. ^d Anal. Calcd.: H₂O, 4.27. Found: H₂O, 3.77 (Karl Fischer).



| Compd. | L | | Yield, % | M.p., °C. | Formula | Calcd., % | | | Found, % | | |
|--------|---|---|----------|-----------|---|-----------------|-------|--------------|-----------------|-------|--------------|
| | | | | | | Cl ⁻ | N | Neut. equiv. | Cl ⁻ | N | Neut. equiv. |
| 1 | C ₆ H ₅ CH ₂ | N(CH ₃) ₂ | 90 | 309–310 | C ₁₄ H ₂₂ N ₂ ·2HCl | 24.34 | 9.62 | 146 | 24.33 | 9.40 | 144 |
| 2 | C ₆ H ₅ CH ₂ | C ₄ H ₉ N ^a | 90 | 44–45 | C ₁₆ H ₂₄ N ₂ ^b | ... | 11.47 | 122 | ... | 11.76 | 122 |
| | | | | 325–329 | ·2HCl | 22.38 | 8.83 | 159 | 22.58 | 9.01 | 159 |
| 3 | C ₆ H ₅ CH ₂ | C ₆ H ₁₀ N ^c | 93 | 317–320 | C ₁₇ H ₂₆ N ₂ ·2HCl | 21.40 | 8.46 | 166 | 21.53 | 8.65 | 164 |
| 4 | H | N(CH ₃) ₂ | 80 | 288–290 | C ₇ H ₁₆ N ₂ ·2HCl | 35.26 | 13.93 | 101 | 35.38 | 13.82 | 100 |
| 5 | H | C ₄ H ₉ N | 83 | 57–59 | C ₉ H ₁₈ N ₂ | ... | 18.16 | 77 | ... | 17.89 | 77 |
| | | | | 335–338 | ·2HCl | 31.21 | 12.33 | 114 | 30.85 | 12.19 | 115 |
| 6 | H | C ₆ H ₁₀ N | 82 | 63–66 | C ₁₀ H ₂₀ N ₂ | ... | 17.24 | 84 | ... | 17.38 | 84 |
| | | | | 346–347 | ·2HCl | 29.40 | 11.61 | 121 | 29.63 | 11.60 | 120 |

^a Pyrrolidino. ^b Synthesized by two different methods (see Experimental Section). ^c Piperidino.



| Compd. ^a | L | R | M.p., °C. | Formula | Calcd., % | | | Found, % | | |
|---------------------|--|----------------------------------|-----------|---|-----------|------|-------|----------|------|-------|
| | | | | | C | H | N | C | H | N |
| 17 | 4-FC ₆ H ₄ CO(CH ₂) ₃ | COCH ₃ | 193–197 | C ₂₃ H ₃₄ FN ₃ O ₂ ·2(COOH) ₂ ·H ₂ O ^b | 53.90 | 6.70 | 6.98 | 53.70 | 6.61 | 7.12 |
| 18 | 4-FC ₆ H ₄ CO(CH ₂) ₃ | COOC ₂ H ₅ | 183.5–185 | C ₂₄ H ₃₆ FN ₃ O ₃ ·2(COOH) ₂ | 54.80 | 6.57 | 6.84 | 54.71 | 6.49 | 6.59 |
| 19 | (C ₆ H ₅) ₂ C(CN)(CH ₂) ₂ | COCH ₃ | 97–101 | C ₂₉ H ₃₆ N ₄ O | 75.94 | 8.35 | 12.17 | 75.78 | 8.41 | 11.90 |
| 20 | (C ₆ H ₅) ₂ C(CN)(CH ₂) ₂ | COOC ₂ H ₅ | 200–202 | C ₃₀ H ₃₈ N ₄ O ₂ ·2(COOH) ₂ | 61.06 | 6.63 | 8.38 | 60.92 | 6.65 | 8.05 |

^a Most of these compounds were synthesized only once and probably not in optimum conditions. Therefore no yield was given. This applies also to Table IV. ^b Anal. Calcd.: H₂O, 2.99. Found: H₂O, 3.49 (Karl Fischer).

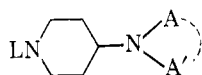
previous series^{1,2} it was found that the compounds obtained in this manner exhibited very interesting pharmacological properties. The choice of substituents in 1-position (L in formula I) was also mainly based on the results obtained in the former series and also in the corresponding pethidine series. It was found that in this series the corresponding compounds are virtually devoid of pronounced hypotensive or CNS-depressant activity. For some of them this is not quite unexpected as the corresponding pethidine counterparts are also inactive. In the case of the butyrophenones **17**, **18**, **26**, and **36**, however, this result was rather disappointing as, for instance, 1-γ-(4-fluorobenzoylpropyl)-4-acetylaminomethyl-4-phenylpiperidine is a potent hypotensive agent. After subcutaneous administra-

tion of 2.5 mg./kg. of this last compound, the carotid blood pressure 1 hr. after dosage is about 67 mm.⁹; for the corresponding compound **17** under the same conditions the blood pressure is 90 mm. and this is statistically not significant with regard to 800 controls (100 mm.). In several other piperidine derivatives these butyrophenones are potent neuroleptic agents; for example the PD₅₀ of haloperidol as an apomorphine antagonist in dogs is 0.02 mg./kg. s.c.,¹⁰ while the butyrophenones of these series (**17**, **18**, **26**, and **36**) are inactive at a dose of 2.5 mg./kg. s.c.

(9) W. K. A. Schaper, A. H. M. Jageneau, and P. A. J. Janssen, *Arznei-mittel-Forsch.*, **13**, 597 (1963).

(10) P. A. J. Janssen, C. J. E. Niemegeers, K. H. L. Schellekens, F. J. Verbruggen, and J. H. Van Nueten, *ibid.*, **13**, 205 (1963).

TABLE IV



| Compd. | L | | M.p., °C. | Formula | Calcd., % | | | | | Neut. equiv. | Found, % | | | | | Neut. equiv. |
|--------|---|---|-----------------|--|-----------|-------|-----------------|-------|-----|-----------------|----------|-------|-----------------|-----|--|-----------------|
| | | | | | C | H | Cl ⁻ | N | | | C | H | Cl ⁻ | N | | |
| 21 | NCCH ₂ | C ₄ H ₈ N ^a | 58-59 | C ₁₁ H ₁₆ N ₃ | 68.35 | 9.91 | ... | 21.74 | 97 | 68.10 | 9.88 | ... | 21.83 | 98 | | |
| 22 | C ₈ H ₁₂ NO ^b | C ₄ H ₈ N | 338-340 | C ₁₅ H ₂₂ N ₃ O · 3HCl | ... | ... | 28.23 | 11.15 | 126 | ... | ... | 28.01 | 11.07 | 119 | | |
| 23 | C ₈ H ₈ (CH ₂) ₂ | C ₄ H ₈ N | 350-351 | C ₁₇ H ₂₆ N ₂ · 2HCl | ... | ... | 21.40 | 8.46 | 166 | ... | ... | 21.46 | 8.69 | 164 | | |
| 24 | C ₈ H ₈ O(CH ₂) ₂ | C ₄ H ₈ N | 308-311 | C ₁₇ H ₂₆ N ₂ O · 2HCl | ... | ... | 20.42 | 8.07 | 174 | ... | ... | 19.98 | 8.02 | 175 | | |
| 25 | C ₈ H ₈ NH(CH ₂) ₂ | C ₄ H ₈ N | 293-300 dec. | C ₁₇ H ₂₇ N ₃ · 3HCl | ... | ... | 27.77 | 10.98 | 191 | ... | ... | 27.33 | 10.86 | 190 | | |
| 26 | 4-FC ₆ H ₄ CO(CH ₂) ₃ | C ₄ H ₈ N | 306-307 | C ₁₉ H ₂₇ FN ₂ O · 2HCl | ... | ... | 18.12 | 7.16 | 196 | ... | ... | 17.87 | 7.22 | 196 | | |
| 27 | (C ₆ H ₅) ₂ CH(CH ₂) ₂ | C ₄ H ₈ N | 335-340 | C ₂₄ H ₃₂ N ₂ · 2HCl | ... | ... | 16.82 | 6.65 | 211 | ... | ... | 16.60 | 6.75 | 211 | | |
| 28 | (C ₆ H ₅) ₂ C(OH)(CH ₂) ₂ | C ₄ H ₈ N | 144-146 | C ₂₄ H ₃₂ N ₂ O | 79.08 | 8.85 | ... | 7.69 | 182 | 78.86 | 8.75 | ... | 7.68 | 185 | | |
| 29 | (C ₆ H ₅) ₂ C(CN)(CH ₂) ₂ | C ₄ H ₈ N | 305-308 | C ₂₈ H ₃₁ N ₃ · 2HCl | ... | ... | 15.88 | 9.41 | 223 | ... | ... | 15.66 | 9.42 | 221 | | |
| 30 | CH ₃ ^c | C ₈ H ₁₆ N ^d | 326-330 | C ₁₁ H ₂₂ N ₂ · 2HCl | ... | ... | 27.79 | 10.98 | 128 | ... | ... | 27.36 | 10.65 | 129 | | |
| 31 | NCCH ₂ | C ₈ H ₁₆ N | 66.8- 67.2 | C ₁₂ H ₂₁ N ₃ | 69.52 | 10.21 | ... | 20.27 | 104 | 69.31 | 10.13 | ... | 20.26 | 104 | | |
| 32 | C ₈ H ₁₂ NO ^c | C ₈ H ₁₆ N | 333-336 | C ₁₆ H ₂₁ N ₃ O · 3HCl | ... | ... | 27.22 | 10.75 | 130 | ... | ... | 27.34 | 10.54 | 132 | | |
| 33 | C ₈ H ₈ (CH ₂) ₂ | C ₈ H ₁₆ N | 344-348 | C ₁₈ H ₂₈ N ₂ · 2HCl | ... | ... | 20.53 | 8.11 | 173 | ... | ... | 20.33 | 8.11 | 175 | | |
| 34 | C ₈ H ₈ O(CH ₂) ₂ | C ₈ H ₁₆ N | 277-297 dec. | C ₁₈ H ₂₈ N ₂ O · 2HCl | ... | ... | 19.62 | 7.75 | 181 | ... | ... | 19.44 | 7.59 | 182 | | |
| 35 | C ₈ H ₈ NH(CH ₂) ₂ | C ₈ H ₁₆ N | 335-340 | C ₁₈ H ₂₉ N ₃ · 3HCl | ... | ... | 26.80 | 10.59 | 198 | ... | ... | 26.80 | 10.40 | 201 | | |
| 36 | 4-FC ₆ H ₄ CO(CH ₂) ₃ | C ₈ H ₁₆ N | 313-315 | C ₂₀ H ₂₉ FN ₂ O · 2HCl | ... | ... | 17.50 | 6.91 | 203 | ... | ... | 17.46 | 7.03 | 199 | | |
| 37 | (C ₆ H ₅) ₂ CH(CH ₂) ₂ | C ₈ H ₁₆ N | +350 | C ₂₈ H ₃₄ N ₂ · 2HCl | ... | ... | 16.28 | 6.43 | 218 | ... | ... | 15.95 | 6.43 | 218 | | |
| 38 | (C ₆ H ₅) ₂ C(OH)(CH ₂) ₂ | C ₈ H ₁₆ N | 125-126 | C ₂₈ H ₃₄ N ₂ O | 79.32 | 9.05 | ... | 7.40 | 189 | 79.09 | 9.05 | ... | 7.63 | 191 | | |
| 39 | (C ₆ H ₅) ₂ C(CN)(CH ₂) ₂ | C ₈ H ₁₆ N | 322-325 | C ₂₈ H ₃₃ N ₃ · 2HCl | ... | ... | 15.40 | 9.13 | 230 | ... | ... | 15.24 | 9.21 | 228 | | |
| 40 | (C ₆ H ₅) ₂ C(CONH ₂)(CH ₂) ₂ ^e | C ₈ H ₁₆ N | 177-178 | C ₂₆ H ₃₆ N ₃ O | 76.99 | 8.70 | ... | 10.36 | 203 | 77.13 | 8.71 | ... | 10.63 | 206 | | |

^a Pyrrolidino. ^b Morpholinoethyl. ^c Synthesized by a reductive alkylation reaction. ^d Piperidino. ^e Synthesized by hydrolysis of **39**.

Experimental Section^{11,12}

1-Benzyl-4-pyrrolidinopiperidine (2). Method A. Reductive Denitration of the α -Aminonitrile.—To a cooled suspension (-5°) of 8.4 g. of LiAlH₄ in 150 ml. of dry ether was added dropwise a solution of 53.8 g. (0.2 mole) of 1-benzyl-4-cyano-4-pyrrolidinopiperidine¹ in 500 ml. of the same solvent. After the addition was complete, the mixture was stirred for 1 hr. at the same temperature and then further stirred for 150 min. at room temperature. The mixture was decomposed by successive addition of 7.5 ml. of water, 6.4 ml. of a 20% NaOH solution, and 30 ml. of water. The formed precipitate was filtered off and washed with ether. The combined organic layers were evaporated and the oily residue was dissolved in 100 ml. of diisopropyl ether. After cooling to -20° , 43 g. of **2**, m.p. 44-45°, was obtained. A hydrochloride salt was formed in ethanol-ether, m.p. 332-334°.

Method B. Reduction of the Enamine. (a) A mixture of 284 g. (1.5 moles) of 1-benzyl-4-piperidone, 135 g. (1.9 moles) of pyrrolidine, and 1300 ml. of benzene, together with a catalytic quantity of *p*-toluenesulfonic acid, was heated under reflux with separation of the formed water. After 4 hr. the calculated amount of water was separated and the mixture was evaporated. The residue was distilled at 153-158° (0.1 mm.) to yield 332 g. (92%) of the 1-benzyl-4-(1-pyrrolidinyl)-1,2,3,6-tetrahydropyridine.

Anal. Calcd.: N, 11.55; neut. equiv., 121. Found: N, 11.63; neut. equiv., 124.

(b) A solution of 24.2 g. (0.1 mole) of the former compound in 250 ml. of methanol was hydrogenated in the presence of 2 g. of 5% palladium on charcoal at atmospheric pressure and at room temperature. When 2400 cc. of hydrogen was absorbed the catalyst was filtered off and the filtrate was evaporated *in vacuo*. The residue was dissolved in 500 ml. of dry ether, and gaseous HCl was introduced. The formed precipitate was filtered off and recrystallized from ethanol-ether to yield 15 g. (47%) of 1-benzyl-4-pyrrolidinopiperidine dihydrochloride, m.p. 331-334° (no melting point depression with the sample of the first method).

1-Benzyl-4-aminomethyl-4-piperidinopiperidine (9).—To a solution of 84 g. of LiAlH₄ in 1000 ml. of dry tetrahydrofuran was added dropwise a solution of 572 g. (1.9 moles) of 1-benzyl-4-piperidino-4-piperidinecarboxamide¹ in 2000 ml. of the same solvent. The reaction was carried out under a nitrogen atmosphere. The mixture was refluxed for 4 hr. and then stirred for 10 hr. at

room temperature, decomposed by successive dropwise addition of 43.5 ml. of water, 32.5 g. of a 20% NaOH solution, and 153 ml. of water, while keeping the temperature below 10°. The whole was filtered and the filter cake was extracted first with 1000 ml. of boiling ether, followed by extraction with 1500 ml. of boiling chloroform. The combined organic solutions were washed with water, evaporated, and distilled at 165° (0.5 mm.) to yield 207 g. of product.

1-Benzyl-4-acetylaminomethyl-4-piperidinopiperidine (10).—To a solution of 160 g. (0.56 mole) of **9** in 800 ml. of dry benzene was added portionwise 610 g. of acetic anhydride. After the addition was complete, the solution was heated to reflux for 1 hr. The whole was then stirred without heating for 2 hr. and evaporated. To the residue was added 300 ml. of water. The aqueous solution was rendered alkaline and extracted with benzene. The organic layer was separated, dried, and evaporated. The residue was crystallized twice from diisopropyl ether to yield 72 g. of **10**, m.p. 82-85°.

1-Benzyl-4-[N-(ethoxycarbonyl)aminomethyl]-4-piperidinopiperidine (11).—To a solution of 28.7 g. (0.1 mole) of **9** in 120 ml. of pyridine was added dropwise a solution of 10.9 g. (0.1 mole) of ethyl chloroformate in 25 ml. of ether. After the addition was complete, the mixture was stirred for 16 hr. at room temperature and then heated for 1 hr. at 60°. After cooling the reaction mixture, the formed precipitate was filtered off. The filtrate was evaporated, the residue was dissolved in dry toluene, and the whole was evaporated again. The residue was dissolved in ether, and gaseous HCl was introduced. The precipitated hydrochloride was filtered off and crystallized from methanol-ether, to yield 19.5 g. of **11**, m.p. 235-237°.

4-Dimethylaminopiperidine (4).—A solution of 58.2 g. (0.2 mole) of 1-benzyl-4-dimethylaminopiperidine dihydrochloride (**1**) in 300 ml. of 2-propanol and 300 ml. of distilled water was hydrogenated in the presence of 6 g. of 10% palladium on charcoal at normal pressure and room temperature. When 4500 cc. of hydrogen had been absorbed, the catalyst was filtered off and the filtrate was evaporated *in vacuo*. The solid residue was recrystallized from methanol-ether, to yield 32 g. (80%) of **4**.

1-(2-Phenethyl)-4-piperidinopiperidine (33).—To a stirred mixture of 3.4 g. (0.02 mole) of 4-piperidinopiperidine (**6**), 6.4 g. (0.06 mole) of Na₂CO₃, and a few crystals of KI in 200 ml. of isobutyl methyl ketone was added dropwise a solution of 3.1 g. (0.022 mole) of phenethyl chloride in 50 ml. of the same solvent. The mixture was then stirred and refluxed for 60 hr. After cooling the reaction mixture was washed with 50 ml. of water. The organic layer was dried and filtered; 300 ml. of anhydrous ether

(11) Analytical data are given in Tables I-IV.

(12) All melting points were taken on a Tottoli melting point apparatus and are corrected.

