4-Substituted Piperidines. IV.[1] The Synthesis of 4-[(2,6-Dioxo-3-phenyl)-3-piperidyl]piperidines

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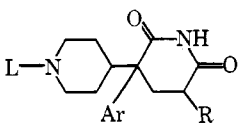
Received August 28, 1967

The synthesis of a new series of 4-substituted piperidine derivatives is described. Some of these compounds, particularly 1-benzyl-4-[(2,6-dioxo-3-phenyl)-3-piperidyl]piperidine, are potent orally active anticholinergics.

In our preceding papers the preparation of several series of 4,4-disubstituted piperidines was described, in which we obtained compounds with different types of pharmacological activity.[1] In the present paper we report an investigation of the possibility of such activity from 4-monosubstituted piperidines also.

It is known from the literature that several drugs possess a 2,6-dioxopiperidine nucleus[2] and these two considerations prompted us to synthesize 4-monosubstituted piperidines of the general formula I, in which Ar represents phenyl, substituted phenyl, or pyridyl, R stands for H or CH_3, and L can be any substituent which does not change the basic character of the piperidine nucleus.

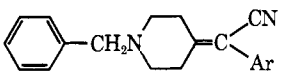


I

Chemistry.—The reaction scheme for the synthesis of these compounds is outlined in Chart I. The first step of the preparation involved the condensation of N-benzyl-4-piperidone with a substituted arylacetonitrile in the presence of sodium methoxide or sodium ethoxide, as described for the corresponding N-methyl analog by Anker[3] and McElvain,[4] respectively. This reaction took place without difficulty for all ten acetonitriles, and compounds II obtained are listed in Table I.

Reduction of these compounds was tried with different catalysts in different solvents, namely with Adams catalyst in acetic acid and with 10% Pd-C in methanol, ethanol, 2-propanol, or acetic acid. In all instances, 2 equiv of hydrogen were taken up and reduction of the double bond could not be performed without debenzylation.[5] The reaction was therefore continued to completion and, after evaporation of the solvent, the crude residue was treated with benzyl chloride to obtain compounds III (see Table II).

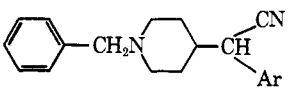
Table I



Compd	Ar	Yield, %	Mp, °C	Formula[a]
1	C_6H_5	68	210–211	$C_{20}H_{20}N_2 \cdot HCl$
2	$4\text{-}FC_6H_4$	55	203–205	$C_{20}H_{19}FN_2 \cdot HCl$
3	$2\text{-}CH_3C_6H_4$	41	239.5–243	$C_{21}H_{22}N_2 \cdot HCl$
4	$3\text{-}CH_3C_6H_4$	59	191–193	$C_{21}H_{22}N_2 \cdot HCl$
5	$4\text{-}CH_3C_6H_4$	52	193–195	$C_{21}H_{22}N_2 \cdot HCl$
6	$4\text{-}C_2H_5C_6H_4$	62	205–208	$C_{22}H_{24}N_2 \cdot HCl$
7	$2,5\text{-}(CH_3)_2C_6H_3$	24	248–251	$C_{22}H_{24}N_2 \cdot HCl$
8	$3,4\text{-}(CH_3)_2C_6H_3$	48	235–238	$C_{22}H_{24}N_2 \cdot HCl$
9	$4\text{-}CH_3OC_6H_4$	53	206–209	$C_{21}H_{22}N_2O \cdot HCl$
10	C_5H_4N[b]	57	192–195	$C_{18}H_{19}N_3 \cdot HCl$

[a] All compounds were analyzed for N, Cl^-, equiv wt. [b] 2-Pyridyl.

Table II



Compd	Ar	Yield, %	Mp, °C	Formula	Analyses[a]
11	C_6H_5	78	75.5–77.5	$C_{20}H_{22}N_2$	N
12	$4\text{-}FC_6H_4$	77	91–93	$C_{20}H_{21}FN_2$	N, F
13	$2\text{-}CH_3C_6H_4$	49	212–214	$C_{21}H_{24}N_2 \cdot HCl$	N, Cl^-
14	$3\text{-}CH_3C_6H_4$	81	Oil[b]	$C_{21}H_{24}N_2$	N
15	$4\text{-}CH_3C_6H_4$	62	212–213	$C_{21}H_{24}N_2 \cdot HCl$	N, Cl^-
16	$4\text{-}C_2H_5C_6H_4$	63	186–190	$C_{22}H_{26}N_2 \cdot HCl$	N, Cl^-
17	$2,5\text{-}(CH_3)_2C_6H_3$	55	223–225	$C_{22}H_{26}N_2 \cdot HCl$	N, Cl^-
18	$3,4\text{-}(CH_3)_2C_6H_3$	55	235–239	$C_{22}H_{26}N_2 \cdot HCl$	N, Cl^-
19	$4\text{-}CH_3OC_6H_4$	62	114–117	$C_{21}H_{24}N_2O$	N
20	C_5H_4N[c]	45	166–170	$C_{19}H_{21}N_3 \cdot 2HCl$	N, Cl^-

[a] All equivalent weights were determined. [b] Used without further purification. [c] 2-Pyridyl.

These basic substituted benzyl cyanides (III) were cyanoethylated with acrylonitrile and once also with methacrylonitrile; when this reaction was performed with Triton B as catalyst, as described by Tagmann, *et al.*,[6] only starting materials were recovered, whereas with sodium ethoxide as condensing agent in dioxane[7] most of these additions proceeded without difficulty. However, for the two compounds (**13**, **17**) in which the phenyl group contains an *ortho* substituent, addition could not be performed in this way and again, only starting materials were isolated.

Catalytic debenzylation of three of the products IV with Pd-C was accomplished with at least 80% yield. The debenzylated compounds V, together with their corresponding tertiary amines IV, are listed in Table III. Ring closure of these pentanedinitriles to the

(1) Part III: B. Hermans, P. Van Daele, C. van de Westeringh, C. Van der Eycken, J. Boey, and P. A. J. Janssen, *J. Med. Chem.*, **9**, 49 (1966).

(2)(a) E. Tagmann, E. Sury, and K. Hoffmann, *Helv. Chim. Acta*, **35**, 1541 (1952); (b) M. A. Davis, S. O. Winthrop, R. A. Thomas, F. Herr, M. P. Charest, and R. Gaudry, *J. Med. Chem.*, **7**, 439 (1964); (c) G. B. Fink and M. R. Juchau, *J. Pharm. Sci.*, **53**, 325 (1964).

(3) R. M. Anker and A. H. Cook, *J. Chem. Soc.*, 806 (1948).

(4) S. M. McElvain and R. E. Lyle, *J. Am. Chem. Soc.*, **72**, 384 (1950).

(5) I. Van Wijngaarden and W. Soudijn [*J. Labelled Compds.*, **1**, 207 (1965)] achieved reduction of the double bond and prevented simultaneous debenzylation under extremely restricted hydrogenation conditions, namely with freshly hydrogenated Adams catalyst in 95% ethanol and in the presence of sodium methoxide.

(6) E. Tagmann, E. Sury, and K. Hoffmann, *Helv. Chim. Acta*, **35**, 1235 (1952).

(7) C. F. Koelsch, *J. Am. Chem. Soc.*, **65**, 437 (1943).

CHART I

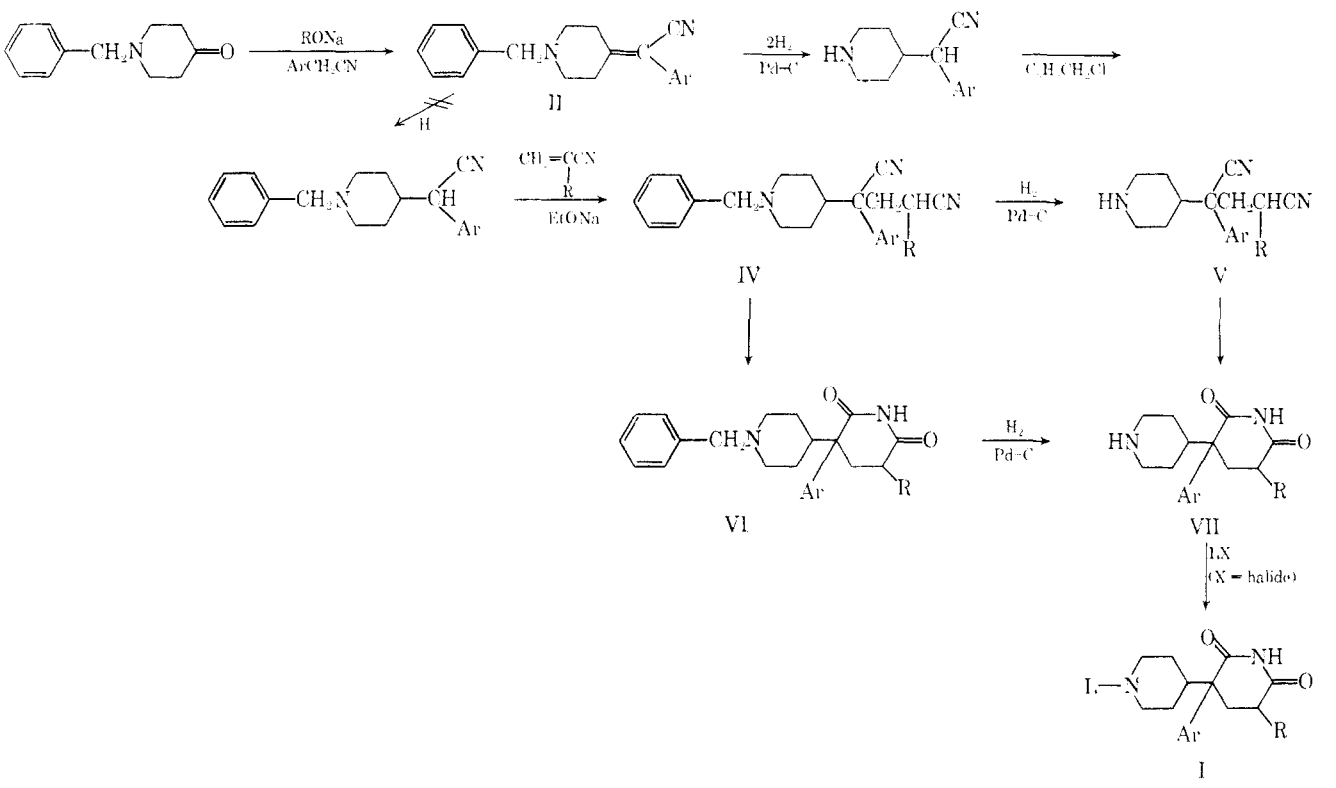
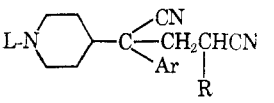


TABLE III



Compd	L	R	Ar	Yield, %	Mp, °C	Formula	Analyses[a]
21	$C_6H_5CH_2$	H	C_6H_5	88	238–241	$C_{23}H_{25}N_3 \cdot HCl$	N, Cl^-
22	$C_6H_5CH_2$	H	4-FC_6H_4	86	234–236	$C_{23}H_{24}FN_3 \cdot HCl$	N, Cl^-
23	$C_6H_5CH_2$	H	3-$CH_3C_6H_4$	73	221–224	$C_{24}H_{27}N_3 \cdot HCl$	N, Cl^-
24	$C_6H_5CH_2$	H	4-$CH_3C_6H_4$	56	246–249	$C_{24}H_{27}N_3 \cdot HCl$	N, Cl^-
25	$C_6H_5CH_2$	H	4-$C_2H_5C_6H_4$	51	226–228	$C_{25}H_{29}N_3 \cdot HCl$	N, Cl^-
26	$C_6H_5CH_2$	H	3,4-$(CH_3)_2C_6H_3$	42	247–250	$C_{25}H_{29}N_3 \cdot HCl$	N, Cl^-
27	$C_6H_5CH_2$	H	4-$CH_3OC_6H_4$	60	248–250	$C_{24}H_{27}N_3O \cdot HCl$	N, Cl^-
28	$C_6H_5CH_2$	H	C_5H_4N[b]	53	149–152	$C_{22}H_{24}N_4 \cdot 2HCl$	N, Cl^-
29	$C_6H_5CH_2$	CH_3	C_6H_5	75	282–284	$C_{24}H_{27}N_3 \cdot HCl$	N, Cl^-
30	H[c]	H	C_6H_5	82	150–152	$C_{16}H_{19}N_3$	N
31	H[c]	H	4-FC_6H_4	92	Oil[d]	$C_{16}H_{18}FN_3$	N
32	H[c]	H	3-$CH_3C_6H_4$	80	Oil[d]	$C_{17}H_{21}N_3$	N

[a] All equivalent weights were determined. [b] 2-Pyridyl. [c] Obtained by debenzylation of the corresponding tertiary amine. [d] Used without further purification.

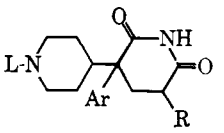
corresponding piperidinediones was carried out on both benzylated (IV) and debenzylated (V) compounds. Ring closure of IV was effected by two different methods. First, by reaction with acetic and sulfuric acid[6] (method A), the free base was liberated but could not easily be purified, and it was therefore necessary to form the hydrochloride salt. In an attempt to avoid these difficulties, ring closure was tried by boiling the dinitrile for about 6 hr with concentrated HCl (method B); from this reaction medium the desired salt crystallized easily. Method B, although much better than A, was only used twice as most ring closures were already accomplished before this HCl method was tried. Hydrogenolysis (method C) of one hydrochloride salt (VI) suspended in ethanol at 50° with Pd–C gave in 80% yield the corresponding secondary amine (VII). Synthesis of the secondary amines (VII) was effected by ring closure of the debenzylated compounds (V); here the reaction with acetic and sulfuric acids was very successful and the free base was obtained very easily. The products (VII), obtained by ring closure of a dinitrile or by hydrogenolysis, are listed in Table IV.

Finally, these secondary amines (VII) were treated with a halide in the presence of sodium carbonate in a mixture of isobutyl methyl ketone and 1-butanol to yield I; the most important of these final products are indicated in Table V.

In the Experimental Section an example of each type of reaction is described.

Pharmacology.—Preliminary screening of benzetimide (**33**), prototype of the current piperidine derivatives,

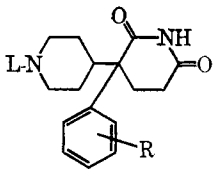
Table IV[a]



Compd	L	R	Ar	Method	Yield, %	Mp, °C	Formula	Analyses[b]
33	$C_6H_5CH_2$	H	C_6H_5	A[c]	53	155–157.6	$C_{23}H_{26}N_2O_2$	N
				B[d]	84	299–301	·HCl	N, Cl^-
34	$C_6H_5CH_2$	H	4-FC_6H_4	A	23	175–185 dec	$C_{23}H_{25}FN_2O_2$·HCl	N, Cl^-, F
35	$C_6H_5CH_2$	H	3-$CH_3C_6H_4$	A	38	108–111	$C_{24}H_{28}N_2O_2$	C, H, N
36	$C_6H_5CH_2$	H	4-$CH_3C_6H_4$	B	88	193–196	$C_{24}H_{28}N_2O_2$·HCl	N, Cl^-
37	$C_6H_5CH_2$	H	4-$C_2H_5C_6H_4$	A	41	156–160	$C_{25}H_{30}N_2O_2$·HCl	N, Cl^-
38	$C_6H_5CH_2$	H	3,4-$(CH_3)_2C_6H_3$	A	32	209–211.5	$C_{25}H_{30}N_2O_2$·HCl	N, Cl^-
39	$C_6H_5CH_2$	H	4-$CH_3OC_6H_4$	A	19	240–248 dec	$C_{24}H_{28}N_2O_3$·HCl	N, Cl^-
40	$C_6H_5CH_2$	H	C_5H_4N[e]	A	27	103–104	$C_{22}H_{25}N_3O_2$	C, H, N
41	$C_6H_5CH_2$	CH_3	C_6H_5	A	29	277–280	$C_{24}H_{28}N_2O_2$·HCl	N, Cl^-
42	H	H	C_6H_5	A	59	230–232	$C_{16}H_{20}N_2O_2$	N
				B	81	295–298	·HCl	N, Cl^-
				C[f]	83	296–298	·HCl	
43	H	H	4-FC_6H_4	A	48	241–242.5	$C_{16}H_{19}FN_2O_2$	N
44	H	H	3-$CH_3C_6H_4$	A	43	190.5–193	$C_{17}H_{22}N_2O_2$	N

[a] Compounds obtained by ring closure of a dinitrile. [b] All equivalent weights were determined. [c] Ring closure of the dinitrile by means of AcOH and H_2SO_4. [d] Ring closure of the dinitrile by boiling in concentrated HCl. [e] 2-Pyridyl. [f] Hydrogenolysis of the benzylamine.

Table V[a]



Compd	L	R	Mp, °C	Formula	Analyses[b]
45	CH_3[c]	H	140–143	$C_{17}H_{22}N_2O_2$	C, H, N
			270–272	·HCl	N, Cl^-
46	n-C_4H_9	H	140–142	$C_{20}H_{28}N_2O_2$	C, H, N
47	n-C_7H_{15}	H	139.5–141.6	$C_{23}H_{34}N_2O_2$	C, H, N
48	3-$ClC_6H_4CH_2$	H	296–298	$C_{23}H_{25}ClN_2O_2$·HCl	N, Cl^-
49	4-$ClC_6H_4CH_2$	H	253–256	$C_{23}H_{25}ClN_2O_2$·HCl	N, Cl^-
50	4-$FC_6H_4CH_2$	H	281–284	$C_{23}H_{25}FN_2O_2$·HCl	N, Cl^-
51	2-$CH_3C_6H_4CH_2$	H	161–163.5	$C_{24}H_{28}N_2O_2$	C, H, N
52	4-$CH_3C_6H_4CH_2$	H	258–260	$C_{24}H_{28}N_2O_2$·HCl	N, Cl^-
53	4-$C_2H_5C_6H_4CH_2$	H	277–280	$C_{25}H_{30}N_2O_2$·HCl	N, Cl^-
54	2,5-$(CH_3)_2C_6H_3CH_2$	H	184.2–186	$C_{25}H_{30}N_2O_2$	C, H, N
55	C_5H_5S[d]	H	266.5–269	$C_{21}H_{24}N_2O_2S$·HCl	N, Cl^-
56	C_6H_6N[e]	H	251–254	$C_{22}H_{25}N_3O_2$·2HCl	N, Cl^-
57	$C_6H_5(CH_2)_2$	H	291–294	$C_{24}H_{28}N_2O_2$·HCl	N, Cl^-
58	$C_6H_5(CH_2)_3$	H	144–146	$C_{25}H_{30}N_2O_2$	C, H, N
59	$C_6H_5CH{=}CH{-}CH_2$	H	157–159	$C_{25}H_{28}N_2O_2$	C, H, N
60	$C_6H_5O(CH_2)_2$	H	88–90	$C_{24}H_{28}N_2O_3$	C, H, N
61	$C_6H_5O(CH_2)_3$	H	145–147	$C_{25}H_{30}N_2O_3$	C, H, N
62	$C_6H_5NH(CH_2)_2$	H	185–190 dec	$C_{24}H_{29}N_3O_2$·$2C_2H_2O_4$	C, H, N
63	$C_6H_5CH{=}CHCH_2$	4-F	212–215	$C_{25}H_{27}FN_2O_2$·HCl·H_2O	N, Cl^-, H_2O
64	$C_6H_5O(CH_2)_2$	4-F	215–217	$C_{24}H_{27}FN_2O_3$·HCl	N, Cl^-
65	$C_6H_5(CH_2)_2$	3-CH_3	305 dec	$C_{25}H_{30}N_2O_2$·HCl	N, Cl^-
66	$C_6H_5O(CH_2)_2$	3-CH_3	222–224	$C_{25}H_{30}N_2O_3$·HCl	N, Cl^-

[a] These compounds were synthesized by alkylation of the secondary amines; most of these reactions were carried out only once and probably not in optimum conditions; therefore no yield is given. [b] All equivalent weights were determined. [c] Prepared by reductive methylation. [d] 2-Thienylmethyl. [e] 2-Pyridylmethyl.

indicated pronounced anticholinergic activity, but no adrenolytic, antihistaminic, or morphine-like properties at therapeutic dose levels.

Anticholinergic activity was investigated for compounds in the present series using the antipilocarpine test in rats.[8] Mydriasis (peripheral action) and the pilocarpine-induced phenomena (salivation, lacrimation (antisecretory action), scratching, hunching, piloerection, tremors, and chewing (central action)) were challenged by each of the test compounds. One hour after subcutaneous administration of the experimental drug, each rat was given a rapid intravenous injection of 80 mg/kg of pilocarpine hydrochloride in H_2O (2 ml/kg). Results are shown in Table VI. Benzetimide

(8) P. A. J. Janssen and C. J. E. Niemegeers, *Psychopharmacologia*, **11**, 231 (1967).

TABLE VI

1-HR ED_{50} VALUES FOR MYDRIATIC (MY), ANTISECRETORY (AS), AND CENTRAL ANTICHOLINERGIC ACTIVITY (CA) AND THE ED_{50} RATIOS FOR THREE COMPOUNDS IN THE PRESENT SERIES AND FOR THREE REFERENCE DRUGS IN AN ANTIPILOCARPINE TEST IN RATS

		ED_{50}, mg/kg			Rel antisecretory potency	Rel central potency
Compd	No.	MY a	AS b	CA c	b/a	c/a
Benzetimide	33	0.060	0.040	0.080	0.67	1.3
Meletimide	52	0.22	0.10	0.30	0.46	1.4
Cinperene	59	0.25	0.13	0.63	0.52	2.5
Atropine		0.016	0.12	0.24	7.5	15
Scopolamine		0.0040	0.010	0.016	2.5	4.0
Benztropine		0.16	0.36	0.24	2.3	1.5

(**33**), meletimide (**52**), and cinperene (**59**) had pronounced peripheral and central activity, and were more potent antisecretory agents (b/a) than were the reference drugs. Their relative central anticholinergic potency (c/a) was very high and comparable with that of benztropine, a clinically accepted antiparkinsonian agent.

In a separate test of anticholinergic properties (inhibition of ulcer formation in starved rats),[9] benzetimide (**33**) was orally active at doses 20 times lower (0.1 mg/rat/day) than for atropine (2 mg/rat/day). Although only half as potent in inducing mydriasis (lowest active dose = 0.6 mg/kg) as atropine (0.3 mg/kg) (see also Table VI), it was much longer acting (16 hr for benzetimide and 2 hr for atropine, after oral administration of a 1-mg/kg dose). It is concluded that compounds in the present series are potent and orally long-acting anticholinergic agents.

Experimental Section[10,11]

1-Benzyl-4-(α-cyanobenzylidene)piperidine (1).—To a solution of NaOEt, prepared from 9.2 g (0.41 g-atom) of Na in 250 ml of EtOH were added successively 37.8 g (0.2 mole) of N-benzyl-4-piperidone and 46.8 g (0.4 mole) of benzyl cyanide. When the addition was completed, the whole was refluxed for 1 hr, cooled, and poured into 1000 ml of ice–water. This solution was acidified with concentrated HCl; the formed precipitate was filtered off and crystallized from MeOH–Et_2O to yield 43.8 g of **1**.

1-Benzyl-4-(α-cyanobenzyl)piperidine (11).—A solution of 32.5 g (0.1 mole) of **1** in 400 ml of MeOH and 150 ml of H_2O was hydrogenated at normal pressure and room temperature in the presence of 5 g of 10% Pd-C. After the calculated amount of H_2 was taken up (0.2 mole), hydrogenation was stopped. The reaction mixture was filtered and evaporated. The residue, together with 12.7 g (0.1 mole) of benzyl chloride and 26.5 g (0.25 mole) of Na_2CO_3, was dissolved in 500 ml of isobutyl methyl ketone and this solution was refluxed for 12 hr. The filtered solution was evaporated, and the solid residue crystallized (*i*-Pr_2O) to yield 22.6 g of **11**.

1-Benzyl-4-[α-cyano-α-(2-cyanoethyl)benzyl]piperidine (21).—To a solution of 72.5 g (0.25 mole) of **11** and 15 g (0.28 mole) of acrylonitrile in 150 ml of dioxane at room temperature were added a few drops of a solution of 2 g of Na in 40 ml of EtOH. The temperature rose 2–3° and this addition was repeated a few times until the temperature reached 30°. By further addition of a few drops of NaOEt, the temperature rose to 55–60°. While this temperature was maintained by cooling, the remaining NaOEt solution was added dropwise. When the addition was complete, the whole was cooled to room temperature and filtered. To the filtrate 100 ml of H_2O was added and the whole was extracted three times with ether. The combined ethereal layers were washed (H_2O), dried (K_2CO_3), and filtered. Gaseous HCl was passed into the filtrate. The formed precipitate was filtered off and crystallized from MeOH to yield 83.5 g of **21**.

4-[α-Cyano-α-(2-cyanoethyl)benzyl]piperidine (30).—A solution of 38 g (0.1 mole) of **21** in 250 ml of MeOH and 25 ml of H_2O was hydrogenated in the presence of 5 g of 10% Pd-C at normal pressure and at about 30°. After 2.5 l. of H_2 was absorbed in about 1 hr, the catalyst was filtered off. The solution was evaporated, and the residue was dissolved in H_2O, made alkaline with NaOH, and saturated with K_2CO_3. The product was extracted ($CHCl_3$), and the organic layer was dried ($MgSO_4$), filtered, and evaporated. The solid residue was crystallized from *i*-PrOH to yield 20.7 g of **30**.

1-Benzyl-4-(2,6-dioxo-3-phenyl-3-piperidyl)piperidine (33). Method A.—Anhydrous AcOH (400 ml) was cooled to about 10°. Then 200 ml of concentrated H_2SO_4 was added dropwise, followed by portionwise addition of 50 g (0.13 mole) of **21**. After the addition was complete, the mixture was heated to 125° within about 15 min and this temperature was maintained for 10 min. After cooling, the reaction mixture was poured onto ice, made alkaline with NH_4OH at 10° and extracted ($CHCl_3$). The $CHCl_3$ layer was washed (twice with 5% Na_2CO_3, twice with H_2O), dried ($MgSO_4$), filtered, and evaporated. The oily residue partly solidified after long scratching in Me_2CO and (*i*-$Pr)_2O$; the solid material was recrystallized from Me_2CO to yield 12 g of **33** (base). The nonsolidified material was dissolved in a mixture of 400 ml of Me_2CO and 750 ml of *i*-Pr_2O; gaseous HCl was passed into the filtrate and the precipitate was filtered off and crystallized from MeOH–H_2O to yield 15 g of **33**·HCl.

Method B.—A mixture of 38 g (0.1 mole) of **21** and 150 ml of concentrated HCl was refluxed for 8 hr; water (150 ml) was added, and the solution was filtered hot. After cooling, the precipitate was filtered off and dried to yield 33.5 g of **33**·HCl.

4-(2,6-Dioxo-3-phenyl-3-piperidyl)piperidine (42).—To 600 ml of anhydrous AcOH, cooled to about 10°, were added first dropwise 300 ml of concentrated H_2SO_4, then portionwise 63.5 g (0.25 mole) of **30**. The whole was heated to 125° within about 30 min and stirring was continued for another 20 min at the same temperature. The reaction mixture was cooled to 20°, poured into 900 g of ice, and made alkaline with NH_4OH at about 20° and then extracted ($CHCl_3$). The organic layer was washed (twice with 5% Na_2CO_3, twice with H_2O), dried ($MgSO_4$), filtered, and evaporated. The solid residue was crystallized from $CHCl_3$ to yield 40.1 g of **42**.

1-Cinnamyl-4-(2,6-dioxo-3-phenyl-3-piperidyl)piperidine (59).—Cinnamyl chloride (3.8 g, 0.025 mole) was added to a stirred mixture of 5.4 g (0.02 mole) of **42**, 5.3 g (0.05 mole) of Na_2CO_3, a few crystals of KI, 125 ml of *n*-BuOH, and 125 ml of 4-methyl-2-pentanone. The whole was stirred and refluxed for 50 hr and, after cooling, 50 ml of H_2O was added. The organic layer was separated, dried (K_2CO_3), filtered, and evaporated. The solid residue was recrystallized (Me_2CO) to give 5 g of **59**.

Acknowledgments.—We are grateful to Mr. F. Sels and Mr. W. Verkest for C, H, and N analyses, and to Mr. P. Demoen for the other analyses. The work described in this publication is part of a program on piperidine derivatives, supported by a grant from the "Instituut tot Aanmoediging van het Wetenschappelijk Onderzoek in Nijverheid en Landbouw (IWONL)."

(9) C. J. E. Niemegeers and P. A. J. Janssen, *J. Pharm. Pharmacol.*, **16**, 26 (1964).

(10) All melting points were taken on a Tottoli melting point apparatus and were corrected. Where analyses are indicated only by symbols of the elements or functions, analytical results obtained for those elements or functions were within ±0.4% of the theoretical values.

(11) Consult tables for analyses performed.