pure product which was used as such in the next step.

1-(4-Chlorophenyl)-2-ethoxy-2-(4-piperidyl)propane Hydrochloride (20). The above crude pyridyl compound (4.6 g, 0.160 mol) was reduced under the conditions described for the preparation of compound 4. The yield was 42%, mp 210–212° (CH_3CN). Anal. ($C_{10}H_{24}ClNO\cdot HCl$) C, H, N.

1-(4-Chlorophenyl)-2-hydroxy-2-(3-piperidyl)butane. The title compound was prepared from the above pyridyl alcohol via the procedure used to prepare 4, mp 148–149.5° (EtOH). Anal. ($C_{17}H_{24}ClNO_2$) C, H, Cl.

1-(4-Chlorophenyl)-2-methoxy-2-[3-(1-acetylpiperidyl)]-butane (22). The title compound was prepared from the above carbinol via the conditions described for the preparation of **19**. The product was an oil which was used as such in the next step.

1-(4-Chlorophenyl)-2-methoxy-2-(3-piperidyl)butane Succinate (23). The above oil was converted to the target compound via the usual hydrolysis conditions. Crystallization from CH_3CN gave mp 137–138°. Anal. ($C_{20}H_{30}ClNO_5$) C, H, Cl, N.

α-(3-Pyridyl)-4-chloroacetophenone (24). To a suspension of phenylsodium (ca. 0.4 mol) in anhydrous benzene at 5° under nitrogen, a solution of diisopropylamine (40 g, 0.4 mol) in anhydrous benzene (40 ml) was added and the mixture was stirred at 5° for 1 h. 3-Picoline (37.2 g, 0.4 mol) diluted with anhydrous benzene (35 ml) was added to the sodium diisopropylamide suspension and the mixture was stirred at 5° for 30 min. A solution of methyl 4-chlorobenzoate (34 g, 0.2 mol) in anhydrous benzene (30 ml) was added and the mixture was stirred at 5° for 1 h. The reaction mixture was poured onto ice with stirring, made strongly acidic with concentrated HCl, and extracted with several portions of benzene to remove any unreacted ester. The aqueous phase was made basic with aqueous 20% sodium hydroxide and extracted with several portions of chloroform. The combined basic extracts were dried (Na_2SO_4) and evaporated in vacuo to give ca. 40 g of a red-brown syrup. Fractional distillation in vacuo (0.2 mm, oil bath 200°) afforded 26.5 g of crude title compound, bp 162–167° (0.2 mm), as an orange syrup that crystallized on standing at room temperature overnight. Trituration with ether gave 23 g of cream-colored solid, mp 59–64°. One additional trituration with ether–petroleum ether (1:1) yielded 21.5 g (47%) of nearly pure ketone, mp 61–64°. An analytical sample, mp 65–68°, was prepared via crystallization from ether–petroleum ether (1:1). Anal. ($C_{13}H_{10}ClNO$) C, H, Cl, N.

1-(3-Piperidyl)-2-(4-chlorophenyl)-2-butanol. The title compound was prepared from the above alcohol according to the procedure described for 4. The yield was 48%, mp 128–131° (CH_3CN). Anal. ($C_{15}H_{22}ClNO$) C, H, Cl, N.

***N*-Acetyl-1-(3-piperidyl)-2-(4-chlorophenyl)-2-butanol.** The title amide was prepared from the above piperidyl alcohol via the usual procedure. The yield was 81%, mp 127–128° ($EtOH–Et_2O$). Anal. ($C_{17}H_{24}ClNO_2$) C, H, N.

1-(3-Piperidyl)-2-(4-chlorophenyl)-2-methoxybutane Succinate (26). The title compound was prepared from the above amide (5.5 g, 0.018 mol) using the procedure described for **11a**. The crude succinate (2.9 g) was recrystallized from CH_3CN to yield the title compound (2.6 g, 36%), mp 145–147°. Anal. ($C_{16}H_{24}ClNO\cdot C_4H_6O_4$) C, H, N.

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Hypoglycemic α-Cycloalkylphenylmethyl, Furanalkyl, and Thiophenealkyl Lactamimides

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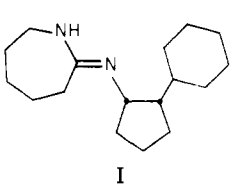
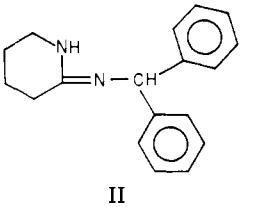
A series of α-cycloalkylphenylmethyl lactamimides and a series of furan- and thiophenealkyl lactamimides were prepared for biological evaluation as an extension of earlier finding of hypoglycemic activity in lactamimides. Compounds **7**, **20**, **23**, **25**, **29**, and **32** produced pronounced hypoglycemia after oral administration to fasted, glucose-primed rats.

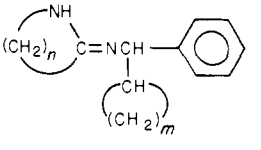
We reported earlier that pronounced hypoglycemic activity is found in lactamimides, in which the α-carbon atom to which the lactamimide function is attached is highly substituted, such as I,[1,2] and in diphenylmethyl-substituted lactamimides, such as II.[3] We now wish to report an attempt to combine these features in compounds of type III, in which the α-carbon atom of phenylmethyl lactamimides is substituted by different cycloalkyl groups,



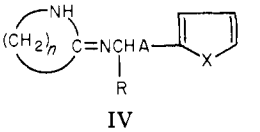
I



II



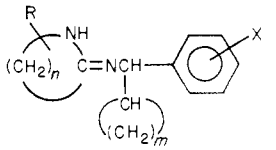
III



IV

and compounds of type IV, in which a phenyl group is replaced by a furan or thiophene ring. The new compounds are listed in Tables I and II.

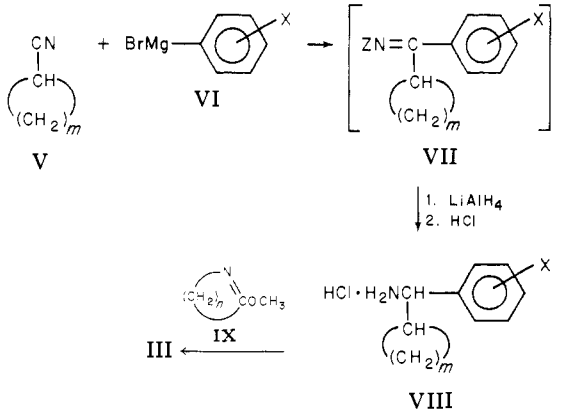
Table I. α-Cycloalkylphenylmethyl Lactamimides. Hypoglycemic Activity in Rats



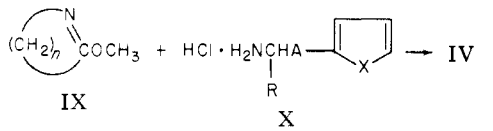
No.	*m*	*n*	X	R	Mp, °C[a]	% yield (reaction time, days)	Mol formula[b]	Plasma glucose (rats)[c] Dose, mg/kg po	Plasma glucose (rats)[c] % reduction vs. control
1	2	4	H	H	174-175 dec	41 (4)	$C_{15}H_{20}N_2$·HCl	100	36
								50	33
								25	23
								12.5	1[d]
2	2	5	H	H	249-250 dec	77 (6)	$C_{16}H_{22}N_2$·HCl	100	51
								50	41
								25	18[e]
								12.5	5[d]
3	2	6	H	H	258-260 dec	52 (50)	$C_{17}H_{24}N_2$·HCl	100	58
								50	46
								25	26
								12.5	0
4	2	5	*p*-OMe	H	192-194	84 (6)	$C_{17}H_{24}N_2O$·HCl	100	40
								12.5	1[d]
5	2	5	*p*-OMe	5-*t*-Bu[f]	232-234 dec	56 (6)	$C_{21}H_{32}N_2O$·HCl	100	17[e]
6	2	5	2,4-Me_2	H	228-230 dec	81 (5)	$C_{18}H_{26}N_2$·HCl	100	56
								50	43
								25	29
								12.5	14[e]
7	2	7	2,4-Me_2	H	217-218 dec	60 (13)	$C_{20}H_{30}N_2$·HCl	100	61
								50	47
								25	37
								12.5	17[e]
8	2	5	2-CH=CH-3[g]	H	292-293 dec	69 (7)	$C_{20}H_{24}N_2$·HCl	100	21
9	3	5	H	H	271-273 dec	79 (5)	$C_{17}H_{24}N_2$·HCl	100	44
								12.5	14[e]
10	4	5	H	H	281-284 dec	82 (4)	$C_{18}H_{26}N_2$·HCl	100	46
								12.5	12[e]
11	5	5	H	H	287-289 dec	82 (7)	$C_{19}H_{28}N_2$·HCl	100	0
12	6	5	H	H	242-244 dec	64 (8)	$C_{20}H_{30}N_2$·HCl	100	6[d]

[a] All compounds were recrystallized from MeOH-Me_2CO. [b] All compounds were analyzed for C, H, and N and results obtained were within ±0.4% of calculated values. [c] Determined by the method of Gerritsen and Dulin with six animals in each treatment group, as described in the Experimental Section. All values over 20% were statistically significant at $p \leq 0.05$. [d] Statistically not significant, $p \geq 0.05$. [e] Statistically significant at $p \leq 0.05$. [f] For preparation of lactim ether IX, $n = 5$, R = 5-*tert*-butyl, see ref 3. [g] α-Naphthyl.

Scheme I



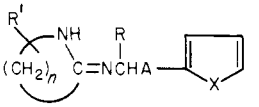
Scheme II



Chemistry. Compounds of type III were prepared as shown in Scheme I. Cycloalkanecarbonitriles V were added to Grignard reagents VI and the resulting imino complexes VII were reduced by addition to lithium aluminum hydride in ether. Amines VIII are listed in Table III. The cyclobutyl and cyclopentyl congeners **38** and **39** were prepared by Leuckart reaction from the corresponding ketones.[4,5] The α-cycloalkylbenzenemethanamine hydrochlorides VIII were allowed to react with lactim ethers IX by a method first described by Benson and Cairns[6] and modified by extending the reaction time at room temperature up to 30 days to overcome steric hindrance.[1]

Compounds of type IV were prepared from amine hydrochlorides X with lactim ethers IX as shown in Scheme II. The amine hydrochlorides **42–46** (Table IV) were available from earlier work in our laboratories.[7,8] The amines **47** and **48** were prepared by reaction of 2-thienylmagnesium bromide with cyclopropanecarbonitrile and benzonitrile, respectively, followed by in situ $LiAlH_4$ reduction. The amine **49** was prepared similarly from 2-furancarbonitrile and phenylmagnesium bromide. The lactamimide **33** was prepared by the method of Bredereck and coworkers[9,10] from 2-azacyclotridecanone, phosphorus

Table II. Furan- and Thiophenealkyl Lactamimides. Hypoglycemic Activity in Rats



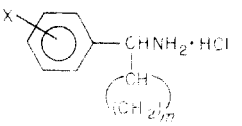
No.	X	*n*	A	R	R′	Mp, °C[a]	% yield (reaction) time, days)	Mol formula[b]	Plasma glucose (rats)[c] Dose, mg/kg po	% reduction vs. control
13	O	5		H	H	150-151	52 (6)	$C_{11}H_{16}N_2O\cdot HCl$	200	0
									100	0
14	S	5		H	H	207-209 dec	67 (4)	$C_{11}H_{16}N_2S\cdot HCl$	100	19[e]
15	S	5	$-CH_2-$	Me	H	178-180	70 (6)	$C_{13}H_{20}N_2S\cdot HCl$	100	41
									12.5	0
16	S	3	$-CH_2-$	Et	H	109-111 dec	51 (28)	$C_{12}H_{18}N_2S\cdot HCl$	100	35
17	S	4	$-CH_2-$	Et	H	134-136 dec	88 (13)	$C_{13}H_{20}N_2S\cdot HCl$	100	42
									12.5	9[d]
18	S	5	$-CH_2-$	Et	H	187-188	82 (8)	$C_{14}H_{22}N_2S\cdot HCl$	100	54
									12.5	10[d]
19	S	6	$-CH_2-$	Et	H	188-190 dec	61 (10)	$C_{15}H_{24}N_2S\cdot HCl$	100	44
20	S	7	$-CH_2-$	Et	H	173-175 dec	53 (12)	$C_{16}H_{26}N_2S\cdot HCl$	100	68
									12.5	31
21	S	5	$-CH_2-$	Et	5-*t*-Bu	223-226 dec	53 (8)	$C_{18}H_{30}N_2S\cdot HCl$	100	32
22	S	5	–CHMe–	Me	H	188-193 dec	74 (6)	$C_{14}H_{22}N_2S\cdot HCl$	100	46
									12.5	0
23	S	5	$-CH_2-$	Allyl	H	143-146 dec	59 (7)	$C_{15}H_{22}N_2S\cdot HCl$	100	65
									50	49
									12.5	14[e]
24	S	4		Cyclopropyl	H	172-174 dec	72 (12)	$C_{13}H_{18}N_2S\cdot HCl$	100	28
25	S	5		Cyclopropyl	H	207-209	73 (7)	$C_{14}H_{20}N_2S\cdot HCl$	100	44
									12.5	33
26	S	6		Cyclopropyl	H	202-204 dec	60 (21)	$C_{15}H_{22}N_2S\cdot HCl$	100	50
									12.5	17[e]
27	O	4		C_6H_5	H	169-171 dec	81 (8)	$C_{16}H_{18}N_2O\cdot HCl$	100	27
									50	28
									25	10[e]
									12.5	13[e]
28	O	5		C_6H_5	H	216-218	77 (5)	$C_{17}H_{20}N_2O\cdot HCl$	100	52
									50	37
									25	34
									12.5	5[d]
29	O	6		C_6H_5	H	255-256 dec	60 (7)	$C_{18}H_{22}N_2O\cdot HCl$	100	61
									50	42
									25	29
									12.5	22
30	S	4		C_6H_5	H	198-200 dec	78 (8)	$C_{16}H_{18}N_2S\cdot HCl$	100	32
									25	31
									12.5	13[d]
31	S	5		C_6H_5	H	255-256 dec	60 (7)	$C_{17}H_{20}N_2S\cdot HCl$	100	50
									50	46
									25	36
									12.5	23[e]
32	S	6		C_6H_5	H	280-281 dec	43 (8)	$C_{18}H_{22}N_2S\cdot HCl$	100	41
									50	37
									25	37
									12.5	29
33	S	11		C_6H_5	H	158-160 dec[f]	27	$C_{23}H_{32}N_2S\cdot HCl$	100	4[d]
I[g]									100	53
									50	49
									25	42
									12.5	33
									6	13[e]
II[h]									100	46
									50	52
									25	42
									12.5	41
									6	12[e]
Tolbutamide									100	41
									50	43
									25	29
									12.5	16[d]

[a-e] See corresponding footnotes in Table I. [f] Recrystallized from *i*-PrOH-H_2O. [g] RMI 11 894A, ref 1. [h] RMI 11 943A, ref 3.

oxychloride, and the amine **48**.

Lactamimides, also named cyclic or semicyclic amidines,[11] occur in two tautomeric forms A and B. This tautomerism has been studied by Kwok and Pranc.[12] For

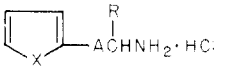
Table III. α-Cycloalkylbenzenemethanamine Hydrochlorides



No.	m	X	Mp, °C[a]	Yield, %	Mol formula	Analyses
34	2	H	224-225 dec[b]	60	$C_{10}H_{13}N·HCl$	C, H, N
35	2	*p*-OMe	213-214	27	$C_{11}H_{15}NO·HCl$	C, H, N
36	2	2,4-Me_2	235-236 dec	24	$C_{12}H_{17}N·HCl$	C, H, N
37	2	2-CH=CH-3[c]	245-247 dec[d]	19	$C_{14}H_{15}N·HCl$	C, H, Cl
38[e]	3	H	311-312 dec	33[f]	$C_{11}H_{15}N·HCl$	
39	4	H	>300[g]	66[f]	$C_{12}H_{17}N·HCl$	
40	5	H	>300	50	$C_{13}H_{19}N·HCl$	C, H, N, Cl
41	6	H	>300	56	$C_{14}H_{21}N·HCl$	C, H, N

[a] Recrystallized from *i*-PrOH-H_2O unless otherwise indicated. [b] A. Burger and H. H. Ong, *J. Org. Chem.*, 29, 2588 (1964), give mp 232-234°. [c] α-Naphthyl. [d] Recrystallized from H_2O. [e] For free base see ref 4. [f] Prepared by Leuckart reaction. [g] Reference 5 gives mp 280°.

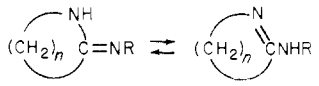
Table IV. Furan- and Thiophenealkylamine Hydrochlorides



No.	X	A	R	Mp, °C (lit. mp)	Yield, %	Mol formula	Analyses
42	S	$-CH_2-$	Me	145-147[a] (139-141)[b]		$C_7H_{11}NS·HCl$	Cl
43	S	$-CH_2-$	Et	112-113[c] (92-93)[d]		$C_8H_{13}NS·HCl$	C, H, N, Cl
44	S	-CHMe-	Me	188-190[a,e]		$C_8H_{13}NS·HCl$	C, H, N, Cl
45	S	$-CH_2-$	$CH_2CH=CH_2$	121-123 (121-123)[f]		$C_9H_{13}NS·HCl$	C, H, N
46	S		Cyclopropyl	210-211 dec[g]	49	$C_8H_{11}NS·HCl$	C, H, N
47	O		C_6H_5	182-183 dec[g,h]	38	$C_{11}H_{11}NO·HCl$	C, H, N
48	S		C_6H_5	264-265 dec[g] (225 dec)[i]	48	$C_{11}H_{11}NS·HCl$	C, H, N

[a] Recrystallized from butanone. [b] F. F. Blicke and J. H. Burckhalter, *J. Am. Chem. Soc.*, 64, 477 (1942). [c] Recrystallized from ethyl acetate. [d] R. T. Gilsdorg and F. F. Nord, *J. Org. Chem.*, 15, 807 (1950). [e] For free base see ref 7. [f] Reference 8. [g] Recrystallized from *i*-PrOH-H_2O. [h] R. Marquis, *C. R. Acad. Sci.*, 129, 112 (1899), and H. Gilman and A. P. Hewlett, *Iowa State Coll. J. Sci.*, 4, 27 (1929) [*Chem. Abstr.*, 24, 1640 (1930)], give no melting point for the HCl salt. [i] R. Duschivsky, U.S. Patent 2 640 835 (1953); *Chem. Abstr.*, 49, 4596 (1954).

the sake of covenience we have represented and named all



A B

compounds in the tautomeric form A. It is not known, however, which form predominates under physiologic conditions.

Biological Evaluation. The compounds listed in Tables I and II were evaluated for hypoglycemic activity in fasted, glucose-primed rats by the method of Gerritsen and Dulin.[13] Of the α-cycloalkylphenylmethyl lactamimides III (Table I) those substituted by cyclopropyl, cyclobutyl, and cyclopentyl groups showed hypoglycemic activity but those substituted by cyclohexyl and cycloheptyl groups did not. Variation of the lactam ring size from six to nine atoms showed only minor effects on hypoglycemic activity. The nine-membered congener **7** was found to be the most active compound. Only a limited number of examples with variation in aromatic substitution were prepared since our studies in the diphenylmethyl series had shown that only *p*-methoxy-substituted congeners show hypoglycemic activity comparable to that of the unsubstituted compounds.[3] This finding was confirmed in the present series (**4** vs. **2**). The 2,4-dimethyl-substituted congeners **6** and **7** were prepared to introduce another steric factor which, indeed, appears to enhance activity slightly.

The group of furan- and thiophenealkyl lactamimides IV (Table II) contains a number of highly active compounds. Of the α-alkyl-2-thiopheneethyl analogs **15–23**, the α-ethyl nine-membered lactam ring congener **20** and the α-allyl seven-membered ring congener **23** were most potent. Of the α-cyclopropyl-2-thiophenemethyl lactamimides **24–26**, the seven-membered lactam ring congener **25** was most active; of the α-phenyl-2-furanmethyl lactamimides **27–29**, the eight-membered ring analog **29** was most active; and of the α-phenyl-2-thiophenemethyl lactamimides **30–33**, the seven- and eight-membered analogs **31** and **32** were most active.

Conclusion

The series of lactamimides of type III and IV contains a number of analogs that are as potent as our previously reported hypoglycemic lactamimides I and II and tolbutamide. In particular, compounds **7**, **20**, **23**, **25**, **29**, and **32** produced marked hypoglycemia. Although this broadens the scope of lactamimides with hypoglycemic activity, structural requirements nevertheless remain within very definite limits and a number of relatively minor structural changes result in loss of this activity.

Experimental Section

Melting points were taken on a Thomas-Hoover capillary melting point apparatus and are corrected. Where analyses are indicated only by the symbols of the elements, analytical results obtained for these elements were within ±0.4% of the theoretical values. Infrared and ultraviolet spectra were obtained for all compounds and were found to be consistent with the assigned structures.

Biological Methods. Plasma Glucose. Hypoglycemic activity was determined by the method of Gerritsen and Dulin.[13] Young male rats of body weight 105–115 g (Sprague–Dawley strain) were fasted overnight. Immediately following subcutaneous administration of 1 g/kg of glucose, test compound was administered by gavage. Later (2 h) blood was withdrawn and plasma glucose was determined by the glucose oxidase procedure.[14]

Plasma glucose concentrations were determined in six treated animals and were compared to those of a control group of six animals that was glucose-primed and administered vehicle only by gavage. The plasma glucose levels of control groups were in the range of 95–100 mg/ml.

N-**(Cyclopropylphenylmethyl)hexahydro-2*H*-azepin-2-imine Hydrochloride (2).** A mixture of 17.0 g (0.093 mol) of powdered **34** (hydrochloride salt) and 17 ml (ca. 0.12 mol) of *O*-methylcaprolactim (IX, $n = 5$)[6,15] was allowed to stand at room temperature for 6 days with occasional stirring. Several 5-ml portions of absolute EtOH were added to keep the mixture stirrable. When the mixture ceased to further solidify, it was cooled (–20°), and the solid was collected, washed with anhydrous Et_2O, and recrystallized from MeOH–Me_2CO to give 19.7 g (77%) of **2** (Table I): ir (KBr) ν_{max} 1650 cm^{-1}.

N-**[Cyclopropyl(2,4-dimethylphenyl)methyl]octahydro-2*H*-azonin-2-imine Hydrochloride (7).** A mixture of 7.0 g (0.033 mol) of powdered **36** (hydrochloride salt) and 7 ml (ca. 0.049 mol) of *O*-methylcapryllactim (IX, $n = 7$)[16] was allowed to stand for 13 days at room temperature. Several 1-ml portions of absolute EtOH were added to keep the mixture stirrable. When the mixture ceased to further solidify, it was cooled (–20°), and the solid was collected, washed with anhydrous Et_2O, and recrystallized twice from MeOH–Me_2CO to give 6.6 g (60%) of **7** (Table I): ir (KBr) ν_{max} 1640 cm^{-1}.

N-**[2-[1-(2-Thienyl)butyl]]pyrrolidin-2-imine Hydrochloride (16).** A mixture of 15.0 g (0.078 mol) of **43** (hydrochloride salt) and 15 ml (ca. 0.105 mol) of *O*-methylbutyrolactim (IX, $n = 3$)[16] was allowed to stand at room temperature for 29 days. After 1 day the mixture had become homogeneous and after 7 days the product started to crystallize from the reaction mixture. The product was collected, washed with anhydrous Et_2O, and recrystallized twice from MeOH–Me_2CO to give 10.4 g (51%) of **16** (Table II): ir (KBr) ν_{max} 1675 cm^{-1}.

N-**[Cyclopropyl(2-thienyl)methyl]hexahydro-2*H*-azepin-2-imine Hydrochloride (25).** A mixture of 16.4 g (0.087 mol) of powdered **46** (hydrochloride salt) and 17 ml (ca. 0.12 mol) of *O*-methylcaprolactim (IX, $n = 5$)[6,15] was allowed to stand at room temperature for 7 days with occasional stirring and addition of several 5-ml portions of absolute EtOH. When the reaction mixture ceased to solidify, it was cooled (–20°), and the solid was collected, washed with anhydrous Et_2O, and recrystallized twice from MeOH–Me_2CO to give 17.7 g (73%) of **25** (Table II): ir (KBr) ν_{max} 1650 cm^{-1}.

Hexahydro-*N*-[(2-thienyl)phenylmethyl]-2*H*-azepin-2-imine Hydrochloride (31). A mixture of 25.0 g (0.111 mol) of powdered 48 (hydrochloride salt) and 25 ml (ca. 0.175 mol) of *O*-methylcaprolactim (IX, $n = 5$)[6,15] was allowed to stand at room temperature for 7 days with occasional stirring and addition of several 5-ml portions of absolute EtOH. When the mixture ceased to solidify, it was cooled (–20°), and the solid was collected, washed with anhydrous Et_2O, and recrystallized twice from MeOH–Me_2CO to give 21.2 g (60%) of **31** (Table II): ir (KBr) ν_{max} 1650 cm^{-1}.

N-**[(2-Thienyl)phenylmethyl]azacyclotridecan-2-imine Hydrochloride (33).** To 6.4 g (0.033 mol) of 2-azacyclotridecanone in 100 ml of C_6H_6 was added 4.8 g (0.031 mol) of $POCl_3$ and the mixture was stirred at room temperature for 4 h. To it was added 6.5 g (0.029 mol) of **48** and the resulting mixture was stirred for 1 h at room temperature and for 4 h at reflux temperature. The resulting solution was allowed to cool overnight, was washed (2 N HCl, saturated NaCl solution), dried (Na_2SO_4), and evaporated to dryness. The resulting oil was crystallized and recrystallized from *i*-PrOH–H_2O to give 3.2 g (27%) of **33** (Table II): ir (KBr) ν_{max} 1645 cm^{-1}.

α-**Cyclopropylbenzenemethanamine Hydrochloride (34).** To C_6H_5MgBr [prepared from 87.0 g (0.555 mol) of C_6H_5Br] in 250 ml of anhydrous Et_2O was added 31.3 g (0.467 mol) of cyclopropanecarbonitrile in 50 ml of anhydrous Et_2O over 1.5 h. The mixture was refluxed for 2 h, was allowed to cool, and was added to a suspension of 21.2 g (0.555 mol) of $LiAlH_4$ in 2.5 l. of anhydrous Et_2O. The resulting mixture was stirred at reflux temperature for 24 h and was decomposed by addition of 21 ml of H_2O, 21 ml of 15% NaOH solution, and 64 ml of H_2O. The resulting inorganic precipitate was filtered off, and the filtrate was dried over Na_2SO_4. Addition of excess ethereal HCl resulted in a precipitate (59.4 g) that was recrystallized from *i*-PrOH–H_2O to give 51.7 g (60%) of **34** (Table III).

α-**Phenylcycloheptanemethanamine Hydrochloride (41).** Starting from 76.3 g (0.486 mol) of C_6H_5Br and 50.0 g (0.407 mol) of cycloheptanecarbonitrile, 88.4 g (91%) of crude **41**, mp >300°, was obtained in the manner described for **34**. After two recrystallizations from *i*-PrOH–H_2O, 52.0 g (56%) of pure **41** (Table III) was obtained.

α-**Cyclopropyl-2-thiophenemethanamine Hydrochloride (46).** Starting from 82.7 g (0.506 mol) of 2-bromothiophene and 28.5 g (0.425 mol) of cyclopropanecarbonitrile, 70.5 g (88%) of crude **46**, mp 204–206° dec, was obtained in the manner described for **34**. After four recrystallizations from *i*-PrOH–H_2O, 39.0 g (49%) of pure **46** (Table IV) was obtained.

2,3,4,5,6,7-Hexahydro-8-methoxyazocine (IX, $n = 6$). To a stirred refluxing solution of 201.9 g (1.6 mol) of octahydroazocin-2-one in 500 ml of C_6H_6 was added dropwise over 4 h 199 g (1.58 mol) of $(CH_3)_2SO_4$. Refluxing was continued overnight. The mixture was cooled in an ice bath and excess 50% K_2CO_3 solution was added cautiously. The C_6H_6 phase was separated, washed with saturated NaCl solution, and dried (Na_2SO_4), and the solvent was evaporated. The residue was distilled: bp 44–48° (1.6 mm) [lit.[17] bp 78° (20 mm)]; 194.7 g (92%); $n^{25}D$ 1.4660.

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