

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<sub>3</sub>CN). Anal. (C<sub>10</sub>H<sub>24</sub>ClNO·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<sub>17</sub>H<sub>24</sub>ClNO<sub>2</sub>) 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<sub>3</sub>CN gave mp 137–138°. Anal. (C<sub>20</sub>H<sub>30</sub>ClNO<sub>5</sub>) 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<sub>2</sub>SO<sub>4</sub>) 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<sub>13</sub>H<sub>10</sub>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<sub>3</sub>CN). Anal. (C<sub>15</sub>H<sub>22</sub>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<sub>2</sub>O). Anal. (C<sub>17</sub>H<sub>24</sub>ClNO<sub>2</sub>) 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<sub>3</sub>CN to yield the title compound (2.6 g, 36%), mp 145–147°. Anal. (C<sub>16</sub>H<sub>24</sub>ClNO·C<sub>4</sub>H<sub>6</sub>O<sub>4</sub>) C, H, N.

**Acknowledgment.** This work was supported by the U.S. Army Medical Research and Development Command under Contract No. DADA-17-69-C-9065. This is Contribution No. 1355 from the Army Research Program on Malaria. The advice and timely suggestions of Drs. T. R. Sweeney, B. T. Poon, and R. E. Strube of the Walter Reed Army Institute of Research are gratefully acknowledged.

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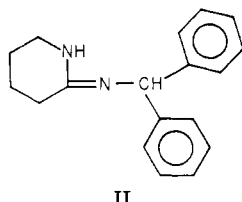
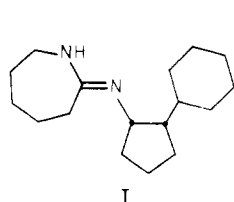
## Hypoglycemic α-Cycloalkylphenylmethyl, Furanalkyl, and Thiophenealkyl Lactamimides

J. Martin Grisar,\* George P. Claxton, and Norbert L. Wiech

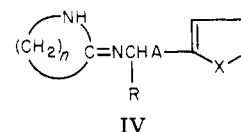
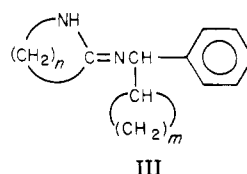
Merrell-National Laboratories, Division of Richardson-Merrell Inc., Cincinnati, Ohio 45215. Received July 31, 1975

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,<sup>1,2</sup> and in diphenylmethyl-substituted lactamimides, such as II.<sup>3</sup> We now wish to

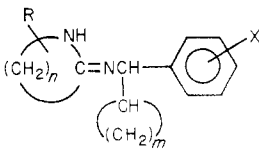


report an attempt to combine these features in compounds of type III, in which the α-carbon atom of phenylmethyl lactamimides is substituted by different cycloalkyl groups,



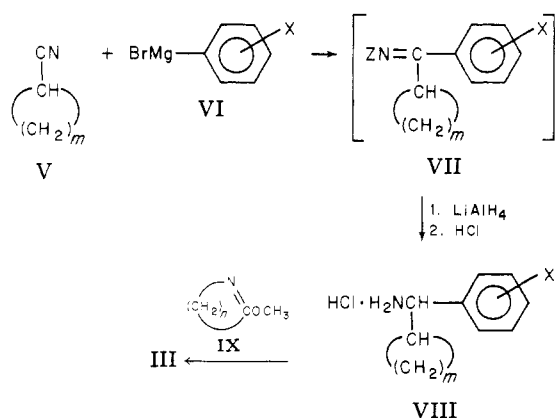
and compounds of type IV, in which a phenyl group is replaced by a furan or thiophene ring. The new compounds are listed in Tables I and II.

Table I.  $\alpha$ -Cycloalkylphenylmethyl Lactamimides. Hypoglycemic Activity in Rats

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

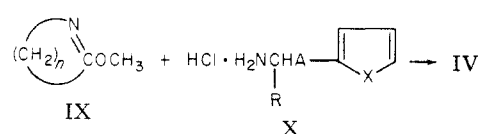
<sup>a</sup> All compounds were recrystallized from MeOH-Me<sub>2</sub>CO. <sup>b</sup> All compounds were analyzed for C, H, and N and results obtained were within  $\pm 0.4\%$  of calculated values. <sup>c</sup> Determined by the method of Gerritsen and Dulin with six animals in each treatment group, as described in the Experimental Section. All values over 20% were statistically significant at  $p \leq 0.05$ . <sup>d</sup> Statistically not significant,  $p > 0.05$ . <sup>e</sup> Statistically significant at  $p \leq 0.05$ . <sup>f</sup> For preparation of lactim ether IX,  $n = 5$ ,  $R = 5$ -*tert*-butyl, see ref 3. <sup>g</sup>  $\alpha$ -Naphthyl.

## Scheme I



**Chemistry.** Compounds of type III were prepared as shown in Scheme I. Cycloalkyl nitriles 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 corre-

## Scheme II



sponding ketones.<sup>4,5</sup> The  $\alpha$ -cycloalkylbenzenemethanamine hydrochlorides VIII were allowed to react with lactim ethers IX by a method first described by Benson and Cairns<sup>6</sup> and modified by extending the reaction time at room temperature up to 30 days to overcome steric hindrance.<sup>1</sup>

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.<sup>7,8</sup> The amines 47 and 48 were prepared by reaction of 2-thienylmagnesium bromide with cyclopropanecarbonitrile and benzonitrile, respectively, followed by in situ LiAlH<sub>4</sub> 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<sup>9,10</sup> from 2-azacyclotridecanone, phosphorus

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

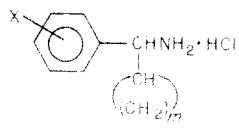
								Plasma glucose (rats) <sup>c</sup>	
								Dose, mg/kg po	% reduc- tion vs. control
No.	X	n	A	R	R'	Mp, °C <sup>a</sup>	% yield (reaction) time, days	Mol formula <sup>b</sup>	
13	O	5		H	H	150-151	52 (6)	C <sub>11</sub> H <sub>16</sub> N <sub>2</sub> O·HCl	200 0
14	S	5		H	H	207-209 dec	67 (4)	C <sub>11</sub> H <sub>16</sub> N <sub>2</sub> S·HCl	100 0
15	S	5	-CH <sub>2</sub> -	Me	H	178-180	70 (6)	C <sub>13</sub> H <sub>20</sub> N <sub>2</sub> S·HCl	100 19 <sup>e</sup>
16	S	3	-CH <sub>2</sub> -	Et	H	109-111 dec	51 (28)	C <sub>12</sub> H <sub>18</sub> N <sub>2</sub> S·HCl	100 41
17	S	4	-CH <sub>2</sub> -	Et	H	134-136 dec	88 (13)	C <sub>13</sub> H <sub>20</sub> N <sub>2</sub> S·HCl	100 0
18	S	5	-CH <sub>2</sub> -	Et	H	187-188	82 (8)	C <sub>14</sub> H <sub>22</sub> N <sub>2</sub> S·HCl	100 35
19	S	6	-CH <sub>2</sub> -	Et	H	188-190 dec	61 (10)	C <sub>15</sub> H <sub>24</sub> N <sub>2</sub> S·HCl	100 42
20	S	7	-CH <sub>2</sub> -	Et	H	173-175 dec	53 (12)	C <sub>16</sub> H <sub>26</sub> N <sub>2</sub> S·HCl	100 9 <sup>d</sup>
21	S	5	-CH <sub>2</sub> -	Et	5- <i>t</i> -Bu	223-226 dec	53 (8)	C <sub>18</sub> H <sub>30</sub> N <sub>2</sub> S·HCl	100 54
22	S	5	-CHMe-	Me	H	188-193 dec	74 (6)	C <sub>14</sub> H <sub>22</sub> N <sub>2</sub> S·HCl	100 10 <sup>d</sup>
23	S	5	-CH <sub>2</sub> -	Allyl	H	143-146 dec	59 (7)	C <sub>15</sub> H <sub>22</sub> N <sub>2</sub> S·HCl	100 44
24	S	4		Cyclopropyl	H	172-174 dec	72 (12)	C <sub>13</sub> H <sub>18</sub> N <sub>2</sub> S·HCl	100 28
25	S	5		Cyclopropyl	H	207-209	73 (7)	C <sub>14</sub> H <sub>20</sub> N <sub>2</sub> S·HCl	100 33
26	S	6		Cyclopropyl	H	202-204 dec	60 (21)	C <sub>15</sub> H <sub>22</sub> N <sub>2</sub> S·HCl	100 50
27	O	4		C <sub>6</sub> H <sub>5</sub>	H	169-171 dec	81 (8)	C <sub>16</sub> H <sub>18</sub> N <sub>2</sub> O·HCl	100 17 <sup>e</sup>
28	O	5		C <sub>6</sub> H <sub>5</sub>	H	216-218	77 (5)	C <sub>17</sub> H <sub>20</sub> N <sub>2</sub> O·HCl	100 27
29	O	6		C <sub>6</sub> H <sub>5</sub>	H	255-256 dec	60 (7)	C <sub>18</sub> H <sub>22</sub> N <sub>2</sub> O·HCl	100 28
30	S	4		C <sub>6</sub> H <sub>5</sub>	H	198-200 dec	78 (8)	C <sub>16</sub> H <sub>18</sub> N <sub>2</sub> S·HCl	100 10 <sup>e</sup>
31	S	5		C <sub>6</sub> H <sub>5</sub>	H	255-256 dec	60 (7)	C <sub>17</sub> H <sub>20</sub> N <sub>2</sub> S·HCl	100 13 <sup>e</sup>
32	S	6		C <sub>6</sub> H <sub>5</sub>	H	280-281 dec	43 (8)	C <sub>18</sub> H <sub>22</sub> N <sub>2</sub> S·HCl	100 52
33 I <sup>g</sup>	S	11		C <sub>6</sub> H <sub>5</sub>	H	158-160 dec <sup>f</sup>	27	C <sub>23</sub> H <sub>32</sub> N <sub>2</sub> S·HCl	100 37
									25 34
									12.5 5 <sup>d</sup>
									100 61
									50 42
									25 29
									12.5 22
									100 32
									25 31
									12.5 13 <sup>d</sup>
									100 50
									50 46
									25 36
									12.5 23 <sup>e</sup>
									100 41
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									12.5 29
									100 4 <sup>d</sup>
									100 53
									50 49
									25 42
									12.5 33
									6 13 <sup>e</sup>
									100 46
									50 52
									25 42
									12.5 41
									6 12 <sup>e</sup>
									100 41
									50 43
									25 29
									12.5 16 <sup>d</sup>

<sup>a-e</sup> See corresponding footnotes in Table I. <sup>f</sup> Recrystallized from *i*-PrOH-H<sub>2</sub>O. <sup>g</sup> RMI 11 894A, ref 1. <sup>h</sup> RMI 11 943A, ref 3.

oxychloride, and the amine 48.

Lactamimides, also named cyclic or semicyclic ami-

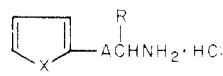
dines,<sup>11</sup> occur in two tautomeric forms A and B. This tautomerism has been studied by Kwok and Pranc.<sup>12</sup> For

Table III.  $\alpha$ -Cycloalkylbenzenemethanamine Hydrochlorides


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

<sup>a</sup> Recrystallized from *i*-PrOH-H<sub>2</sub>O unless otherwise indicated. <sup>b</sup> A. Burger and H. H. Ong, *J. Org. Chem.*, **29**, 2588 (1964), give mp 232-234°. <sup>c</sup>  $\alpha$ -Naphthyl. <sup>d</sup> Recrystallized from H<sub>2</sub>O. <sup>e</sup> For free base see ref. 4. <sup>f</sup> Prepared by Leuckart reaction. <sup>g</sup> Reference 5 gives mp 280°.

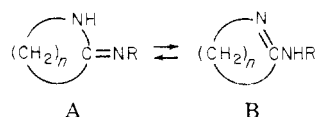
Table IV. Furan- and Thiophenealkylamine Hydrochlorides



No.	X	A	R	Mp, °C (lit. mp)	Yield, %	Mol formula	Analyses
42	S	-CH <sub>2</sub> -	Me	145-147 <sup>a</sup> (139-141) <sup>b</sup>		C <sub>7</sub> H <sub>11</sub> NS·HCl	Cl
43	S	-CH <sub>2</sub> -	Et	112-113 <sup>c</sup> (92-93) <sup>d</sup>		C <sub>8</sub> H <sub>13</sub> NS·HCl	C, H, N, Cl
44	S	-CHMe-	Me	188-190 <sup>a,e</sup>		C <sub>8</sub> H <sub>13</sub> NS·HCl	C, H, N, Cl
45	S	-CH <sub>2</sub> -	CH <sub>2</sub> CH=CH <sub>2</sub>	121-123 (121-123) <sup>f</sup>		C <sub>9</sub> H <sub>13</sub> NS·HCl	C, H, N
46	S		Cyclopropyl	210-211 dec <sup>g</sup>	49	C <sub>8</sub> H <sub>11</sub> NS·HCl	C, H, N
47	O		C <sub>6</sub> H <sub>5</sub>	182-183 dec <sup>g,h</sup>	38	C <sub>11</sub> H <sub>11</sub> NO·HCl	C, H, N
48	S		C <sub>6</sub> H <sub>5</sub>	264-265 dec <sup>g</sup> (225 dec) <sup>i</sup>	48	C <sub>11</sub> H <sub>11</sub> NS·HCl	C, H, N

<sup>a</sup> Recrystallized from butanone. <sup>b</sup> F. F. Blicke and J. H. Burckhalter, *J. Am. Chem. Soc.*, **64**, 477 (1942). <sup>c</sup> Recrystallized from ethyl acetate. <sup>d</sup> R. T. Gilsdorg and F. F. Nord, *J. Org. Chem.*, **15**, 807 (1950). <sup>e</sup> For free base see ref. 7. <sup>f</sup> Reference 8. <sup>g</sup> Recrystallized from *i*-PrOH-H<sub>2</sub>O. <sup>h</sup> 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. <sup>i</sup> R. Duschinsky, U.S. Patent 2 640 835 (1953); *Chem. Abstr.*, **49**, 4596 (1954).

the sake of convenience we have represented and named all



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.<sup>13</sup> Of the  $\alpha$ -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.<sup>3</sup> 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  $\alpha$ -alkyl-2-thiopheneethyl analogs 15-23, the  $\alpha$ -ethyl nine-membered lactam ring congener 20 and

the  $\alpha$ -allyl seven-membered ring congener 23 were most potent. Of the  $\alpha$ -cyclopropyl-2-thiophenemethyl lactamimides 24-26, the seven-membered lactam ring congener 25 was most active; of the  $\alpha$ -phenyl-2-furanmethyl lactamimides 27-29, the eight-membered ring analog 29 was most active; and of the  $\alpha$ -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  $\pm 0.4\%$  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.<sup>13</sup> 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.<sup>14</sup>

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-2H-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)<sup>6,15</sup> 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<sub>2</sub>O, and recrystallized from MeOH–Me<sub>2</sub>CO to give 19.7 g (77%) of 2 (Table I): ir (KBr)  $\nu_{\max}$  1650 cm<sup>–1</sup>.

**N-[Cyclopropyl(2,4-dimethylphenyl)methyl]octahydro-2H-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)<sup>16</sup> 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<sub>2</sub>O, and recrystallized twice from MeOH–Me<sub>2</sub>CO to give 6.6 g (60%) of 7 (Table I): ir (KBr)  $\nu_{\max}$  1640 cm<sup>–1</sup>.

**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)<sup>16</sup> 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<sub>2</sub>O, and recrystallized twice from MeOH–Me<sub>2</sub>CO to give 10.4 g (51%) of 16 (Table II): ir (KBr)  $\nu_{\max}$  1675 cm<sup>–1</sup>.

**N-[Cyclopropyl(2-thienyl)methyl]hexahydro-2H-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)<sup>6,15</sup> 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<sub>2</sub>O, and recrystallized twice from MeOH–Me<sub>2</sub>CO to give 17.7 g (73%) of 25 (Table II): ir (KBr)  $\nu_{\max}$  1650 cm<sup>–1</sup>.

**Hexahydro-N-[(2-thienyl)phenylmethyl]-2H-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)<sup>6,15</sup> 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<sub>2</sub>O, and recrystallized twice from MeOH–Me<sub>2</sub>CO to give 21.2 g (60%) of 31 (Table II): ir (KBr)  $\nu_{\max}$  1650 cm<sup>–1</sup>.

**N-[(2-Thienyl)phenylmethyl]azacyclotridecan-2-imine Hydrochloride (33).** To 6.4 g (0.033 mol) of 2-azacyclotridecanone in 100 ml of C<sub>6</sub>H<sub>6</sub> was added 4.8 g (0.031 mol) of POCl<sub>3</sub> 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<sub>2</sub>SO<sub>4</sub>), and evaporated to dryness. The resulting oil was crystallized and recrystallized from *i*-PrOH–H<sub>2</sub>O to give 3.2 g (27%) of 33 (Table II): ir (KBr)  $\nu_{\max}$  1645 cm<sup>–1</sup>.

**$\alpha$ -Cyclopropylbenzenemethanamine Hydrochloride (34).** To C<sub>6</sub>H<sub>5</sub>MgBr [prepared from 87.0 g (0.555 mol) of C<sub>6</sub>H<sub>5</sub>Br] in 250 ml of anhydrous Et<sub>2</sub>O was added 31.3 g (0.467 mol) of cyclopropanecarbonitrile in 50 ml of anhydrous Et<sub>2</sub>O 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<sub>4</sub> in 2.5 l. of anhydrous Et<sub>2</sub>O. The resulting mixture was stirred at reflux temperature for 24 h and was decomposed by addition of 21 ml of H<sub>2</sub>O, 21 ml of 15% NaOH solution, and 64 ml of H<sub>2</sub>O. The resulting inorganic precipitate was filtered off, and the filtrate was dried over Na<sub>2</sub>SO<sub>4</sub>. Addition of excess ethereal HCl resulted in a precipitate (59.4 g) that was recrystallized from *i*-PrOH–H<sub>2</sub>O to give 51.7 g (60%) of 34 (Table III).

**$\alpha$ -Phenylcycloheptanemethanamine Hydrochloride (41).** Starting from 76.3 g (0.486 mol) of C<sub>6</sub>H<sub>5</sub>Br 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<sub>2</sub>O, 52.0 g (56%) of pure 41 (Table III) was obtained.

**$\alpha$ -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<sub>2</sub>O, 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<sub>6</sub>H<sub>6</sub> was added dropwise over 4 h 199 g (1.58 mol) of (CH<sub>3</sub>)<sub>2</sub>SO<sub>4</sub>. Refluxing was continued overnight. The mixture was cooled in an ice bath and excess 50% K<sub>2</sub>CO<sub>3</sub> solution was added cautiously. The C<sub>6</sub>H<sub>6</sub> phase was separated, washed with saturated NaCl solution, and dried (Na<sub>2</sub>SO<sub>4</sub>), and the solvent was evaporated. The residue was distilled: bp 44–48° (1.6 mm) [lit.<sup>17</sup> bp 78° (20 mm)]; 194.7 g (92%); *n*<sub>D</sub><sup>25</sup> 1.4660.

**Acknowledgment.** We thank Mr. L. Allen and associates for preparation of starting materials, Mr. T. Holman for assistance in the biological evaluations, and Mr. M. J. Gordon and associates for microanalyses and spectra.

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