# Hypoglycemic Cycloalkyl Lactamimides

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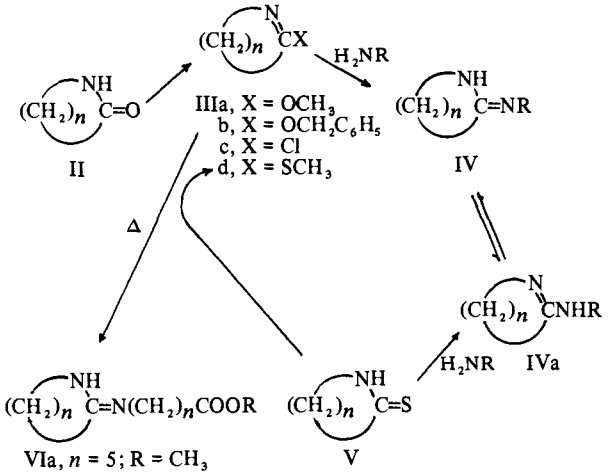
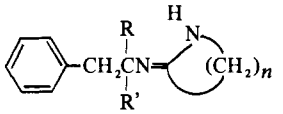
2-[(*cis*-2-Cyclohexylcyclopentyl)imino]hexahydroazepine hydrochloride (**15**) (RMI 11,894) has been prepared and was found to be a potent hypoglycemic agent. Its synthesis resulted from the observation that steric hindrance at the α-carbon atom in noncyclic (I) and cyclic alkyl lactamimide series (IX–XIII) enhances hypoglycemic activity. The use of "lethargic" reaction conditions made it possible to overcome the detrimental effect of steric hindrance on the reactivity of the primary amines with lactim ethers in the synthesis of 2-substituted cycloalkyl lactamimides XIII. Variation of ring size of the cycloalkyl and of the lactam moieties, respectively, exploration of substituents, and examination of cis,trans pairs of isomers resulted in the selection of 15 as a preclinical candidate.

We reported earlier on some lactamimides.[1] Some of these compounds were subsequently found to possess hypoglycemic activity. Since lactamimides (structure IV in Scheme I)† contain an amidine function, the finding of hypoglycemic activity brought to mind the early work on antidiabetic agents resulting in decamethylenediguanide (synthalin) and phenethylbiguanide (phenformin).[3,4] These agents, however, contain guanyl or biguanyl groups, not simple amidine or cyclic amidine functions. After reconfirming the initial finding of hypoglycemic activity and ascertaining that it was dose-related and not subject to tachyphylaxis, it was decided to further explore this discovery.

Scheme I



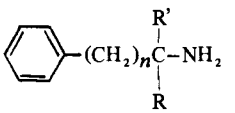

Our first attempts to delineate the structural requirements for hypoglycemic activity in lactamimides were based on the observation that Ia[5] had no activity, Ib[6,‡] had some, and Ic had a strong hypoglycemic effect. These compounds differ in the degree of substitution at the α-carbon atom, *i.e.*, the carbon atom to which the lactamimide function is attached, and increased activity paralleled an increase in steric hindrance. We therefore set out to synthesize other sterically hindered lactamimides. We soon found that the feasibility of preparing such compounds is limited, and it became necessary to explore several available synthetic methods for their ability to overcome steric hindrance.



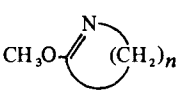
Ia, R = H; R' = H; *n* = 5
b, R = Me; R' = H; *n* = 5
c, R = Me; R' = Me; *n* = 5
d, R = Me; R' = Me; *n* = 3

Several methods for the preparation of lactamimides are known.[7] These are outlined in Scheme I. Several reagents, all derived from the parent lactam II, can be employed. The most conveninet method is that of Benson and Cairns,[8] in which lactim ethers IIIa are used. Bredereck and coworkers[9,10] explored in detail the reaction of complexes of lactams with $POCl_3$, $COCl_2$, $Me_2SO_4$, and $BF_3$, including the iminochlorides IIIc, with primary amines. The use of thiolactams V has been reported,[11] and thiolactim ethers IIId have been used successfully.[12,13] In all of these reactions the primary amine may be used as the hydrochloride salt or as the free base.[14]

To explore the application of these methods to the preparation of sterically hindered lactamimides, we thoroughly investigated the reaction of VIIa·HCl with lactim ethers VIII. Reaction of VIIa·HCl with the five-membered lactim ether VIIIa proceeded smoothly, while reaction with the six-, seven-, or eight-membered lactim ethers VIIIb-d gave little or no product. When VIIa·HCl and excess VIIIc in EtOH were refluxed for 1 hr or for 4 days no reaction products were isolated. The use of anhydrous EtOH and strict exclusion of moisture did not improve the result. When the mixture was heated without a solvent to 100° or to its boiling point (157°) for 4 days, none of the desired product was obtained. In addition to recovery of starting material VIIa that was readily identified by ir, the formation of an ester group containing side product was observed that, in one case, was isolated and identified as compound VIa. Thus, some caprolactim (VIIIc) had opened to methyl ε-aminocaproate, which reacted further with VIIIc to give VIa.



VIIa, *n* = 1; R = R' = $CH_3$
b, *n* = 1; R, R' = $-(CH_2)_4-$
c, *n* = 1; R, R' = $-(CH_2)_5-$
d, *n* = 1; R, R' = $-(CH_2)_6-$
e, *n* = 2; R, R' = $-(CH_2)_5-$



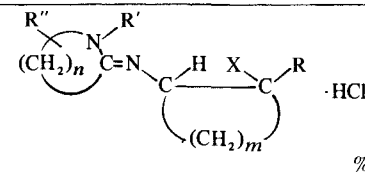
VIIIa, *n* = 3
b, *n* = 4
c, *n* = 5
d, *n* = 6

Pearson and Keaton[15] found that the oximation of sterically hindered ketones can be accomplished by prolonged reaction at room temperature in what they termed a "lethargic reaction" and defined as "a reaction that proceeds slowly but cannot be forced because of incursion of

†For the sake of convenience, all lactamimides are shown and named here in one of two possible tautomeric forms IV ⇌ IVa; *cf.* ref 2.

‡Prepared by Dr. E. M. Roberts who initiated our interest in lactam imides; *cf.* ref 1.

Table I. Substituted Cycloalkyl Lactamimides. Hypoglycemic Activity



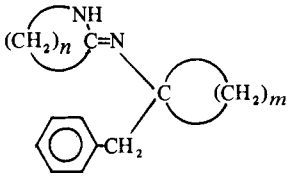

| No. | R | R' | R" | X | m | Isomer | n | Mp, °C[a] | % yield[b] (reaction time, days) | Mol formula[c] | Plasma glucose, rats[d] Dose, mg/kg po | % reduction |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | $C_6H_5$ | H | H | H | 1 | Trans | 5 | 232–233 | 64 (1) | $C_{15}H_{20}N_2 \cdot HCl$ | 100 | 12[f] |
| 2 | $C_6H_5$ | H | H | H | 2 | Trans | 5 | 225–226 | 64 (21) | $C_{16}H_{22}N_2 \cdot HCl$ | 100 | 12[f] |
| 3 | $C_6H_5$ | H | H | H | 3 | Cis | 5 | 182–184 dec | 71 (6) | $C_{17}H_{24}N_2 \cdot HCl$ | 100 | 36 |
| | | | | | | | | | | | 50 | 42 |
| | | | | | | | | | | | 12.5 | 18[e] |
| 4[g] | $C_6H_5$ | H | H | H | 3 | Trans | 5 | 192–193 | 76 (3) | $C_{17}H_{24}N_2 \cdot HCl$ | 100 | 29 |
| 5 | $C_6H_5$ | H | H | H | 4 | Trans | 5 | 236–239 | 74 (28) | $C_{18}H_{26}N_2 \cdot HCl$ | 100 | 13[e] |
| 6 | $C_6H_5$ | H | H | H | 5 | Trans | 5 | 234–235 | 66 (21) | $C_{19}H_{28}N_2 \cdot HCl$ | 100 | 23 |
| 7 | $C_6H_5$ | H | H | H | 5 | Cis | 5 | 207–211 | 53 (20) | $C_{19}H_{28}N_2 \cdot HCl$ | 100 | 51 |
| | | | | | | | | | | | 50 | 19[e] |
| | | | | | | | | | | | 25 | 9[f] |
| 8 | $C_6H_5$ | $CH_2C_6H_5$ | H | H | 3 | Cis | 3 | 158–166 | 33[h] | $C_{22}H_{26}N_2 \cdot HCl$ | 100 | 36 |
| 9 | $C_6H_5$ | H | H | H | 3 | Cis | 4 | 173–176 | 80 (5) | $C_{16}H_{22}N_2 \cdot HCl$ | 100 | 34 |
| 10 | $C_6H_5$ | H | H | H | 3 | Cis | 7 | 207–209 dec | 36 (16) | $C_{19}H_{28}N_2 \cdot HCl$ | 100 | 60 |
| 11 | $C_6H_5$ | H | H | H | 3 | Cis | 11 | 156–159 | 46[h] | $C_{23}H_{36}N_2 \cdot HCl$ | 100 | 5[f] |
| 12 | $C_6H_5$ | H | 5-*tert*-Bu | H | 3 | Cis | 5 | 291–293 dec | 28 (3) | $C_{21}H_{32}N_2 \cdot HCl$ | 100 | 9[f] |
| 13 | $C_6H_5$ | H | H | OH | 3 | ? | 5 | 261–262 | 59 (41) | $C_{17}H_{24}N_2O \cdot HCl$ | 100 | 45 |
| | | | | | | | | | | | 50 | 2[f] |
| | | | | | | | | | | | 25 | 0 |
| 14 | $C_6H_4Cl$-*p* | H | H | H | 3 | Cis | 5 | 253–255 | 75 (40) | $C_{17}H_{23}ClN_2 \cdot HCl$ | 100 | 24 |
| 15[o] | $C_6H_{11}$[i] | H | H | H | 3 | Cis | 5 | 179–180 dec | 51 (31) | $C_{17}H_{30}N_2 \cdot HCl$ | 100 | 53 |
| | | | | | | | | | | | 50 | 49 |
| | | | | | | | | | | | 25 | 42 |
| | | | | | | | | | | | 12.5 | 33 |
| | | | | | | | | | | | 6 | 15[e] |
| 16 | $C_6H_{11}$[i] | H | H | H | 3 | Trans | 5 | 208–210 | 49 (40) | $C_{17}H_{30}N_2 \cdot HCl$ | 100 | 46 |
| 17 | $C_6H_{11}$[i] | H | H | H | 3 | Cis | 4 | 196–197 | 62 (24) | $C_{16}H_{28}N_2 \cdot HCl$ | 100 | 49 |
| | | | | | | | | | | | 50 | 41 |
| | | | | | | | | | | | 12.5 | 31 |
| | | | | | | | | | | | 6 | 2[f] |
| 18 | $C_6H_{11}$[i] | H | H | H | 3 | Cis | 6 | 216–219 dec | 24 (29) | $C_{18}H_{32}N_2 \cdot HCl$ | 100 | 62 |
| | | | | | | | | | | | 50 | 53 |
| | | | | | | | | | | | 25 | 41 |
| | | | | | | | | | | | 12.5 | 0 |
| | | | | | | | | | | | 6 | 8[f] |
| 19 | $C_5H_9$[j] | H | H | H | 3 | Mixture | 5 | 178–182 | 48 (33) | $C_{16}H_{28}N_2 \cdot HCl$ | 100 | 66 |
| 20 | 2-$C_4H_3S$[k] | H | H | H | 3 | Mixture | 5 | 144–151 | 20 (42) | $C_{15}H_{22}N_2S \cdot HCl$ | 100 | 36 |
| Ia[l,n] | | | | | | | 5 | 183–184 | 86 | $C_{14}H_{20}N_2 \cdot HCl$ | 100 | 6[f] |
| Ib[g,m,n] | | | | | | | 5 | 182–183 | 62 | $C_{15}H_{22}N_2 \cdot HCl$ | 100 | 30 |
| Ic[n] | | | | | | | 5 | 217–218 | 9 (29) | $C_{16}H_{24}N_2 \cdot HCl$ | 100 | 63 |
| | | | | | | | | | | | 50 | 29 |
| | | | | | | | | | | | 25 | 17[e] |
| | | | | | | | | | | | 12.5 | 0 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Id[n] | 3 | 175–177 dec | 49 (7) | $C_{14}H_{20}N_2 \cdot HCl$ | 100 | 31 | |
| IXa[n] | 3 | 216–217 | 42 (26) | $C_{16}H_{22}N_2 \cdot HCl$ | 100 | 50 | |
| | | | | | 50 | 46 | |
| | | | | | 25 | 25 | |
| | | | | | 12.5 | 20[e] | |
| | | | | | 6 | 7[f] | |
| X[n] | 5 | 314–316 dec | 64 (1) | $C_{13}H_{22}N_2 \cdot HCl$ | 100 | 22 | |
| XIa[n] | 3 | >300 | 60 (35) | $C_{14}H_{22}N_2 \cdot HCl$ | 100 | 6[f] | |
| XIb[n] | 4 | >300 | 48 (45) | $C_{15}H_{24}N_2 \cdot HCl$ | 100 | 22 | |
| XIc[n] | 5 | >300 | 31 (47) | $C_{16}H_{26}N_2 \cdot HCl$ | 100 | 16[e] | |
| XIIa[n] | 3 | >300 | 53 (9) | $C_{14}H_{22}N_2 \cdot HCl$ | 100 | 23 | |
| XIIc[n] | 5 | >300 | 60 (12) | $C_{16}H_{26}N_2 \cdot HCl$ | 100 | 0 | |
| Tolbutamide | | | | | 100 | 41 | |
| | | | | | 50 | 43 | |
| | | | | | 25 | 29 | |
| | | | | | 12.5 | 16[f] | |

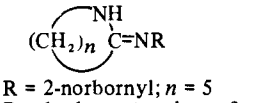
[a]Melting points are corrected and were taken on a Hoover capillary melting point apparatus. All compounds were recrystallized from MeOH–$Me_2CO$, except IXa, XIa–c, and 13 which were recrystallized from EtOH, and 8 which was recrystallized from $CH_2Cl_2$–$Et_2O$. [b]Yields refer to purified product. For procedure see Experimental Section and discussion of lethargic reaction in the text. [c]All compounds were analyzed for C, H, and one other element. Analytical results obtained for these elements were within ±0.4% of the calculated values. [d]Groups of six young male Sprague–Dawley rats were fasted overnight and primed with 100 mg sc of glucose immediately after dosing by stomach tube, and plasma glucose was determined 2 hr later. All values of over 20% reduction of plasma glucose were statistically significant at $p \leq 0.05$. [e]Statistically significant at $p \leq 0.05$. [f]Statistically not significant, $p \geq 0.05$. [g]See footnote ‡. [h]Prepared by the procedure described for compound 11 in the Experimental Section. [i]Cyclopentyl. [k]2-Thienyl. [l]Reference 5. [m]Reference 6. [n]See structure in text. [o]See footnote §.

side reactions at elevated temperatures." Following this idea, we allowed a mixture of finely powdered VIIa·HCl and excess VIIIc to stand at room temperature for 29 days and were able to obtain Ic. The yield was 9% of theory. All efforts to improve this yield were futile, as were attempts to obtain a product of VIIa with the six- and eight-membered lactim ethers VIIIb and VIIId. Lethargic reaction of VIIa·HCl with *O*-benzyllactim ether IIIb ($n = 5$) or with the thiolactim ether IIId ($n = 5$), both of which are expected to be more reactive reagents, did not result in improved yields of Ic. The use of Bredereck's procedure[9,10] in which caprolactam (II, $n = 5$), activated by $POCl_3$, $COCl_2$, or a combination of both was used in $Et_2O$, $C_6H_6$, or $Cl(CH_2)_2Cl$, or prolonged reaction of thiocaprolactam (V, $n = 5$) in the presence of HgO by the procedure of Gautier and Renault[11] failed to give improved yields.

To further explore the feasibility of preparing highly sterically hindered lactamimides, we investigated the reaction of the 1-benzylcycloalkylamines VIIb-d[16] and of 1-phenethylcyclohexylamine VIIe, with lactims VIIIa–c under lethargic reaction conditions. The only product we were able to obtain in this series was IXa. This result indicated that the cyclic amines VIIb–e are more sterically hindered than VIIa. In this case, however, we did not go to such length in exploring reaction conditions and compounds IX in which $m$ and $n$ are larger than 4 and 3, respectively, may have formed in low yield (<10%) but defied isolation. Compound IXa showed strong hypoglycemic activity (as shown at the bottom of Table I). It was more active than the noncyclic analog Id and this finding further confirmed the validity of our approach of examining the effect of steric hindrance at the α-carbon atom on hypoglycemic activity. The 2-norbornyl and the 1- and 2-adamantanyl lactamimides X–XII were obtained without difficulty but showed less hypoglycemic effect.

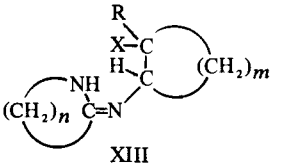


IXa, $m = 4$; $n = 3$



Xc, R = 2-norbornyl; $n = 5$
XIa, R = 1-adamantanyl; $n = 3$
b, R = 1-adamantanyl; $n = 4$
c, R = 1-adamantanyl; $n = 5$
XIIa, R = 2-adamantanyl; $n = 3$
c, R = 2-adamantanyl; $n = 5$

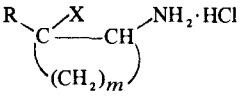
Fortuitously, we had a series of 2-substituted cycloalkylamines available for preparation of compounds of structure XIII. In this series we had the unique opportunity to control the steric environment of the α-carbon atom by variation of the size of the cycloalkyl ring ($m$) as well as that of the lactam ring ($n$), in addition to variation of R, and comparison of cis and trans isomers. The compounds prepared are listed in Table I.



XIII

The compounds listed in Table I were obtained in generally good yields under lethargic reaction conditions. Column 10 in Table I gives yields and reaction times (in days). It is possible, after some experience, to observe during this heterogenous reaction the disappearance of starting amine·HCl and the precipitation of product and to thereby

Table II. Substituted Cycloalkylamine Hydrochlorides



| No. | R | X | m | Isomer | Mp, °C[a] | Lit. mp, °C | Mol formula[b] |
|---|---|---|---|---|---|---|---|
| **21** | $C_6H_5$ | H | 2 | Trans | 211–213 | 210–213[c] | $C_{10}H_{13}N\cdot HCl$ |
| **22** | $C_6H_5$ | H | 3 | Cis | 204–206 | 189–192[d] | $C_{11}H_{15}N\cdot HCl$ |
| **23** | $C_6H_5$ | H | 3 | Trans | 147–149 | 144–145[e] | $C_{11}H_{15}N\cdot HCl$ |
| **24** | $C_6H_5$ | H | 4 | Trans | 251–257 | 253[f] | $C_{12}H_{17}N\cdot HCl$ |
| **25** | $C_6H_5$ | H | 5 | Trans | 229–230 | 227–229[g] | $C_{13}H_{19}N\cdot HCl$ |
| **26** | $C_6H_5$ | H | 5 | Cis | 199–200 | 197–198[h] | $C_{13}H_{19}N\cdot HCl$ |
| **27** | $C_6H_5$ | OH | 3 | ? | 199.5 dec | *i* | $C_{11}H_{15}NO\cdot HCl$ |
| **28** | *p*-$ClC_6H_4$ | H | 3 | Cis | 226–229 | | $C_{11}H_{14}ClN\cdot HCl$ |
| **29** | $C_6H_{11}$[j] | H | 3 | Cis | 174–176 | | $C_{11}H_{21}N\cdot HCl$ |
| **30** | $C_6H_{11}$[j] | H | 3 | Trans | 199–200 | | $C_{11}H_{21}N\cdot HCl$ |
| 31 | $C_5H_9$[k] | H | 3 | Mixture | 175–194 | | $C_{10}H_{19}N\cdot HCl$[l] |
| **32** | 2-$C_4H_3S$[m] | H | 3 | Mixture | 115–172 | *n* | $C_9H_{13}NS\cdot HCl$ |
| VIIb[p] | | | | | 206–209 | *o* | $C_{12}H_{17}N\cdot HCl$ |
| VIIc[p] | | | | | 297–299 | *o* | $C_{13}H_{19}N\cdot HCl$ |
| VIId[p] | | | | | 240–243 | | $C_{14}H_{21}N\cdot HCl$ |
| VIIe[p] | | | | | 209–211 | | $C_{14}H_{21}N\cdot HCl$ |

[a,b] See footnotes *a* and *c*, Table I. [c] Reference 19. [d] References 18 and 20. [e] Reference 20. [f] See ref 20; also J. v. Braun, H. Gruber, and G. Kirschbaum, *Ber.*, **55**, 3664 (1922); R. T. Arnold and P. N. Richardson, *J. Amer. Chem. Soc.*, 76, 3649 (1954). [g] References 20 and 21. [h] Reference 21. [i] *Cf.* F. G. Bordwell and E. W. Garbisch, Jr., *J. Org. Chem.*, **28**, 1765 (1963). [j] Cyclohexyl. [k] Cyclopentyl. [l] No elemental analysis was obtained; ir (KBr) 1970 $cm^{-1}$. Obtained by catalytic hydrogenation over Rh/C in $NH_3$–MeOH of 2-cyclopentylcyclopentanone oxime, mp 75–77° [lit. mp 78–79°: H. Christol, M. Mousseron, and R. Sallé, *Bull. Soc. Chim. Fr.*, 556 (1958)]. [m] 2-Thienyl. [n] Reference 18. [o] Free base prepared as described in ref 16. [p] See structure in text.

estimate when the reaction is complete. The data on yields and reaction time therefore give an approximate indication of reaction rate and degree of steric hindrance. The amine salts that were used are listed in Table II. They were prepared some time ago as part of a program related to cypenamine.[17,18] The stereochemistry of these amines has since been established by Burger and coworkers.[19–21]

**Biological Activity and Structure-Activity Relationships.** Hypoglycemic activity was determined by the method of Gerritsen and Dulin.[22] Young male rats of body weight 145–155 g (Sprague-Dawley strain) were fasted overnight. Six animals were given a glucose load of 100 mg sc immediately after dosing of the test compound by a stomach tube. Two hours later blood was withdrawn and plasma glucose was determined by the glucose oxidase procedure.[23] The results are recorded in the last column of Table I.

Several compounds show potent hypoglycemic activity. These are, in addition to Ic and IXa, compounds **3**, **7**, **10**, **13**, and **15–19**. Variation of the cycloalkyl ring (compounds **1–7**) shows that the cyclopropyl, cyclobutyl, and cyclohexyl congeners ($m$ = 1, 2, and 4) have little or no activity, while cyclopentyl and cycloheptyl congeners ($m$ = 3 and 5) are active. Comparison of trans isomers reveals little difference between cyclopentyl and cycloheptyl congeners **4** and **6**, but comparison of the cis isomers clearly shows the cyclopentyl congener **3** superior to **7**. The cis isomer **3** is more active than the trans isomer **4**. Consequently, all further structural modifications were carried out in the *cis*-cyclopentyl series. Variation of the R group shows phenyl less active than cyclohexyl (**3** *vs.* **15**). Aromatic halogen substitution was found to be detrimental (**14**). The cyclopentyl-substituted congener **19** was more active than the thiophene-substituted compound **20** but since both are mixtures of isomers, the comparison may not be valid. The optimum size of the lactam ring was found to be $n$ = 5 (*cf.* **15** *vs.* **17** and **18**) and substitution on the lactam ring was found to diminish activity (**12**). The seven-membered lactam congener **15**§ was found to significantly lower plasma glucose levels in rats at 6 mg/kg po. It is therefore about four times more potent than our initial lead Ic and about twice as active as IXa. Compound **15**§ is being prepared for clinical trial.

## Experimental Section#

**2-[(α,α-Dimethylphenethyl)imino]pyrrolidine Hydrochloride (Id).** To 10.0 g of finely powdered α,α-dimethylphenethylamine hydrochloride (VIIa) was added 15 ml of *O*-methylbutyrolactim (VIIIa) and the mixture was stirred into a slurry and allowed to stand at room temperature. After 5 days the mixture became completely homogeneous and after 7 days the product separated as crystals. It was collected and recrystallized twice from $Me_2CO$–MeOH to give Id, $\nu$ (KBr) 1670 $cm^{-1}$ (Table I).

**2-[(1-Benzylcyclopentyl)imino]pyrrolidine Hydrochloride (IXa).** To 12.0 g of 1-benzylcyclopentylamine hydrochloride (VIIb, Table II) was added 10 ml of *O*-methylbutyrolactim (VIIIa); the reactants were mixed thoroughly and allowed to stand at room temperature. After 13 days the mixture had become nearly homogeneous while crystalline product started to separate. Small portions of additional VIIIa were added to keep the mixture in a stirrable slurry. After 26 days the mixture was cooled to −20° and the precipitate was collected and recrystallized twice from $Me_2CO$–MeOH and once from anhydrous EtOH to give IXa, $\nu$ (KBr) 1675 $cm^{-1}$ (Table I).

**2-(1-Adamantanylimino)piperidine Hydrochloride (Xb).** A slurry of 15.0 g of 1-adamantanamine hydrochloride and 25 ml of *O*-methylvalerolactim (VIIIb) was allowed to stand at room temperature for 45 days with occasional stirring. The product was collected, washed with anhydrous $Et_2O$, and recrystallized once from $Me_2CO$ and once from EtOH to give XIb (Table I).

**Hexahydro-2-[(*trans*-2-phenylcyclopentyl)imino]azepine Hydrochloride (4).**‡ To a solution of 10.0 g (0.051 mol) of *trans*-2-phenylcyclopentylamine hydrochloride (**23**, Table II) in 25 ml of anhydrous EtOH was added 7.2 ml (0.053 mol) of *O*-methylcaprolactim (VIIIc)[8] with stirring. The resulting solution was allowed to stand at room temperature for 3 days. The solution was then poured into 1 l. of $Et_2O$; the resulting oil was separated by decantation, crystallized, and was recrystallized from $Me_2CO$–MeOH to give 4, $\nu$ (KBr) 1645 $cm^{-1}$ (Table I).

**2-[(*cis*-2-Cyclohexylcyclopentyl)imino]hexahydroazepine Hydrochloride (15).** A thoroughly mixed slurry of 3.5 g of *cis*-2-cyclohexylcyclopentylamine hydrochloride (**29**, Table II) and *O*-methylcaprolactim (VIIIc) was allowed to stand at room temperature for 31 days with occasional stirring. After 14 days the mixture

§ Also known as RMI 11,894.

#See footnotes *a* and *c* to Table I.

began to stiffen and 1 ml of anhydrous EtOH was added to keep the slurry stirrable; this process was repeated several times. The product was collected and recrystallized twice from $Me_2CO$–MeOH to give **15**, $\nu$ (KBr) 1650 $cm^{-1}$ (Table I).

**2-[(*cis*-2-Phenylcyclopentyl)imino]azacyclotridecane Hydrochloride (11).** To 21.7 g (0.11 mol) of 2-azacyclotridecanone in 200 ml of dried $C_6H_6$ was added dropwise 15.3 g (0.10 mol) of $POCl_3$. The mixture was stirred at room temperature for 4 hr after which 19.8 g (0.1 mol) of *cis*-2-phenylcyclopentylamine hydrochloride (**22**, Table II) was added. The mixture was stirred at room temperature for 2 hr and at reflux temperature for 24 hr and became homogeneous. The $C_6H_6$ solution was washed with 2 *N* HCl and saturated NaCl solution and dried ($Na_2SO_4$), and the solvent was evaporated. The resulting oil was crystallized from $Me_2CO$ and recrystallized twice from $Me_2CO$–MeOH to give **11**, $\nu$ (KBr) 1645 $cm^{-1}$ (Table I).

**1-Benzylcycloheptylamine Hydrochloride (VIId).**** *Caution! The reaction described in the following was carried out in a closed vessel equipped with a gas trap containing dilute NaOH to neutralize any HCN that might escape.* To an ice-cooled solution of 92.0 g (0.45 mol) of 1-benzylcycloheptanol and 71.1 g (1.45 mol) of NaCN in 240 ml of AcOH was added dropwise over 30 min 110 ml of concentrated $H_2SO_4$. The mixture was stirred overnight and allowed to warm to room temperature. It was poured into 2 l. of ice–NaOH, containing sufficient base to neutralize the acids. The product was extracted into $CHCl_3$, the extract was washed (2 *N* NaOH, $H_2O$) and dried ($MgSO_4$), the solvent was evaporated, and the product recrystallized from cyclohexane to give 58.2 g (56%) of *N*-(1-benzylcycloheptyl)formamide, mp 102–105°. *Anal.* ($C_{15}H_{21}NO$) C, H, N.

A solution of 35.6 g of the above material in 90 ml of EtOH and 80 ml of 10% NaOH was refluxed for 48 hr. The solvents were evaporated, $H_2O$ was added, and the product was extracted into $Et_2O$. The extract was washed with $H_2O$ and 2 *N* HCl at which point the product precipitated. Recrystallization from *i*-PrOH gave 18.5 g (50%) of VIId, mp 240–243° (Table II).

***cis*- and *trans*-2-Cyclohexylcyclopentylamine Hydrochloride (29 and 30).** Hydrogenation of 12.6 g of *cis*-2-phenylcyclopentylamine hydrochloride, mp 204–206° (**22**, Table II), in 100 ml of $H_2O$ over Rh/C (4.0 g) in a Parr shaker at room temperature required 20 hr. The catalyst was removed by filtration, the filtrate was made basic with dilute NaOH, and the product was extracted into ether. It was distilled, bp 100–102° (60 mm), converted to the HCl salt, and recrystallized to give 4.4 g of cis isomer **29**, mp 174–176° (Table II).

Hydrogenation of *trans*-2-phenylcyclopentylamine hydrochloride, mp 142–143° (**23**, Table II), gave *trans*-2-cyclohexylcyclopentylamine hydrochloride (**30**), mp 199–200° (Table II).

**Methyl 6-(Hexahydroazepin-2-ylidinamino)caproate Hydrochloride (VIa).** From one of the reaction mixtures of VIIa and VIIIc, the title compound was isolated and recrystallized twice from $Me_2CO$–MeOH, mp 86–89°. *Anal.* ($C_{13}H_{24}N_2O_2 \cdot HCl$) C, H, N.

***O*-Benzylcaprolactim (IIIb, *n* = 5).**†† A mixture of 190.8 g (1.5 mol) of *O*-methylcaprolactim and 324.4 g (3.0 mol) of $C_6H_5CH_2OH$ was heated slowly over 5.5 hr in a distillation apparatus until the pot temperature reached 220°; MeOH was allowed to distill. After the mixture was allowed to cool it was distilled first at 14 mm to remove excess $C_6H_5CH_2OH$ and then at 3 mm to obtain product. The fraction, bp 138–149° (3 mm), $n^{26}D$ 1.5321, 267.0 g (82%), was collected.

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## References

(1) E. M. Roberts, J. M. Grisar, R. D. MacKenzie, G. P. Claxton, and T. R. Blohm, *J. Med. Chem.*, **15**, 1270 (1972).
(2) R. Kwok and P. Pranc, *J. Org. Chem.*, **32**, 738 (1967).
(3) F. N. Fastier, *Pharmacol. Rev.*, **14**, 37 (1962).
(4) A. Kreutzberger, *Fortschr. Arzneimittelforsch.*, 11, 356 (1968).
(5) K. Gätzi, Swiss Patent 412,463 (1966); *Chem. Abstr.*, 61, 16055 (1964).
(6) W. A. Behrendt, *Arch. Int. Pharmacodyn. Ther.*, **147**, 99 (1964).
(7) H. Schnell and J. Nentwig, "Houben-Weyl, Methoden der Organischen Chemie," Vol. 11, Part 2, E. Müller, Ed., Georg Thieme Verlag, Stuttgart, 1958, pp 577–578.
(8) R. E. Benson and T. L. Cairns, *J. Amer. Chem. Soc.*, **70**, 2115 (1948); "Organic Syntheses," Collect. Vol. IV, Wiley, New York, N. Y., 1963, p 588.
(9) H. Bredereck and K. Bredereck, *Chem. Ber.*, **94**, 2278 (1961).
(10) H. Bredereck, F. Effenberger, and G. Simchen, *ibid.*, **97**, 1403 (1964).
(11) J. A. Gautier and J. Renault, *C. R. Acad. Sci.*, **234**, 2081 (1952).
(12) H. Behringer and H. Meier, *Justus Liebigs Ann. Chem.*, **607**, 73 (1957).
(13) L. I. Barsky and W. L. Bencze, *J. Med. Chem.*, **14**, 40 (1971).
(14) A. Etienne and Y. Correia, *Bull. Soc. Chim. Fr.*, 3704 (1969).
(15) D. E. Pearson and O. D. Keaton, *J. Org. Chem.*, **28**, 1557 (1963).
(16) H. Christol, A. Laurent, and M. Mousseron, *Bull. Soc. Chim. Fr.*, 2313 (1961).
(17) A. A. Kurland, H. J. Dorf, M. H. Michaux, and J. B. Goldberg, *Curr. Ther. Res.*, 9, 293 (1967).
(18) G. J. Van Zoeren, U. S. Patent 2,520,516 (1950); *Chem. Abstr.*, **45**, 647 (1951).
(19) C. Beard and A. Burger, *J. Org. Chem.*, **26**, 2335 (1961).
(20) C. Kaiser, B. M. Lester, C. L. Zirkle, A. Burger, C. S. Davis, T. J. Delia, and L. Zirngibl, *J. Med. Pharm. Chem.*, **5**, 1243 (1962).
(21) A. Burger, C. R. Walter, Jr., W. B. Bennet, and L. B. Turnbull, *Science*, **112**, 306 (1950).
(22) G. C. Gerritsen and W. E. Dulin, *Diabetes*, 14, 507 (1965).
(23) L. P. Cawley, F. E. Spear, and R. Kendall, *Amer. J. Clin. Pathol.*, **32**, 195 (1959).

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