3-(10,11-Dihydro-*N*,*N*,5-trimethyl-5*H*-dibenzo[*a*,*d*]cycloheptene-4)-propylamine (13).—Reaction of **22** (7.0 g) with LAH (7.0 g) in boiling THF (200 ml) for 3 hr afforded the product (5.0 g) after chromatog on alumina (activity II) and elution with C_6H_6. The oily free base was converted to the maleate salt, which had mp 154–156° (MeCN–Et_2O). *Anal.* ($C_{25}H_{31}NO_4$) C, H, N.

Acknowledgment.—The authors wish to thank Mr. A. Aviram for technical assistance.

cis-1-[2-(*p*-Anisidinomethyl)cyclohexyl]piperidine and Related Compounds. Oral Hypoglycemic Agents

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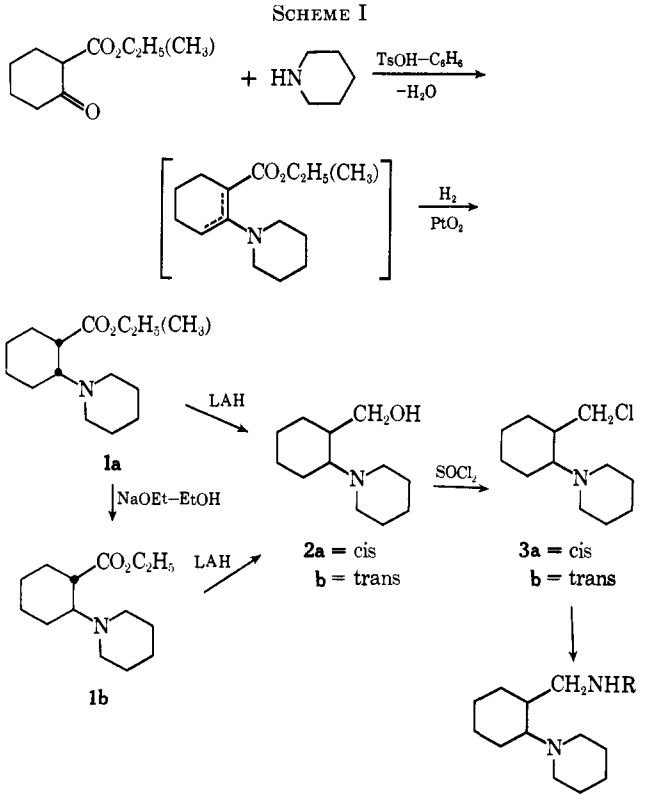
The synthesis and hypoglycemic activity of *cis*-1-[2-(*p*-anisidinomethyl)cyclohexyl]piperidine (**13**), a representative of a new class of hypoglycemic agents, are described. A structure–activity relationship study involving the preparation and hypoglycemic testing of 13 compounds related to **13** is described.

Screening for antidiabetic agents revealed that *cis*-1-[2-(*p*-anisidinomethyl)cyclohexyl]piperidine dihydrochloride (**13**, Table I), possessed good hypoglycemic activity in the glucose-primed, fasted, intact rat. This compd is representative of a class of compounds not previously associated with hypoglycemic activity. As a result, a study aimed at obtaining insight into the various structural features necessary for hypoglycemic activity in this class of compounds was made.

Chemistry.—Compds **4a**, **4b**, and **5** (Table I) were prepared according to the synthetic sequence outlined in Scheme I. Compds **4a** and **4b** were also prepared by

SCHEME I

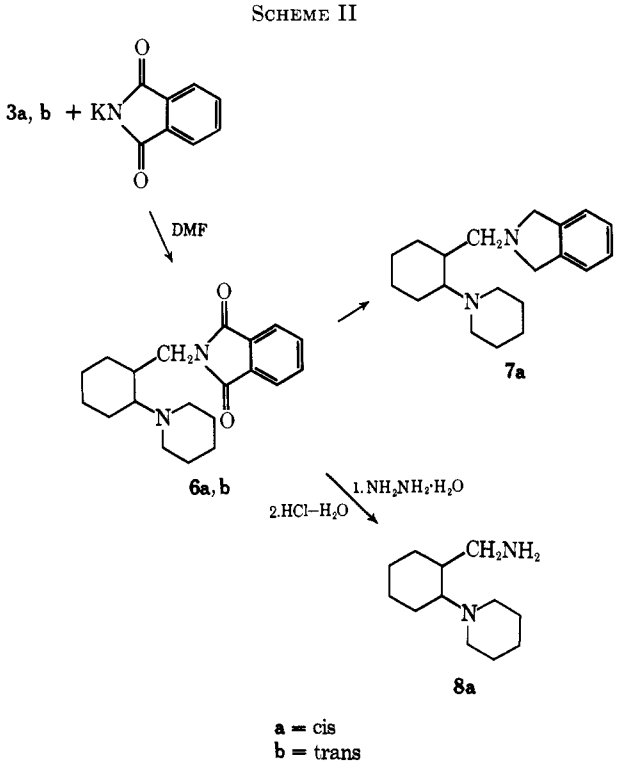


the LAH reduction of the appropriate amides (see Experimental Section).

Treatment of a mixture of ethyl and methyl 2-cyclohexanonecarboxylates with piperidine in benzene, according to the method of Stork and coworkers,[1] afforded a mixture of α,β-unsaturated amines[2] which was hydrogenated, using PtO_2 catalyst, to afford **1a**. The cis isomer **1a** was isomerized to the trans isomer **1b** with NaOEt in EtOH. Reduction of **1a** and **1b** with LAH afforded the alcohols **2a** and **2b** which were subsequently converted into the desired synthetic intermediates **3a** and **3b** with $SOCl_2$. Treatment of **3a** and **3b** with the appropriate primary amine and K_2CO_3 in PhMe afforded **4a–5**.

Compds **6a–8** were prepared according to Scheme II.

SCHEME II

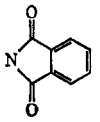
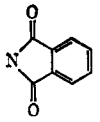
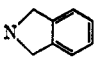


Treatment of **3a** and **3b** with potassium phthalimide in DMF afforded the phthalimides **6a** and **6b** in good

(1) G. Stork, A. Brizzolara, H. Landesman, J. Szmuszkovicz, and R. Terrell, *J. Amer. Chem. Soc.*, **85**, 207 (1963).

(2) The nmr spectrum showed this to be a mixture of the Δ1 and Δ2 isomers.

TABLE I

No.	*n*	Isomer	NR_1R_2	Mp, °C	Recrystn solvent	Formula	Analysis	Relative act.[a]
4a	2	cis	NHC_6H_5	255–257	EtOH	$C_{18}H_{28}N_2 \cdot 2HCl$	C, H, N	0.8
4b	2	trans	NHC_6H_5	163–164 dec	Et_2O–EtOH	$C_{18}H_{28}N_2 \cdot 2HCl \cdot 0.5C_2H_6O$	C, H, N, Cl	1.0
5	2	cis	$NHCH_2C_6H_4OCH_3$-*p*	246.5–247.5	EtOH	$C_{20}H_{32}N_2O \cdot HCl$	C, H, N	0.5–1.0
6a	2	cis		181.5–182.5	EtOH	$C_{20}H_{26}N_2O_2$	C, H, N	0.0
6b	2	trans		180.5–181.5	EtOH	$C_{20}H_{26}N_2O_2$	C, H, N[b]	0.0
7a	2	cis		264–266	Et_2O–MeOH	$C_{20}H_{30}N_2 \cdot 2HCl$	C, H, N, Cl	1.2
8a	2	cis	NH_2	278.5–280	Et_2O–EtOH	$C_{12}H_{24}N_2 \cdot 2HCl \cdot 0.33C_2H_6O$	C, H, N, Cl	0.0
9	2	cis	NHC_6H_{11}	321–322	EtOH	$C_{18}H_{34}N_2 \cdot 2HCl$	C,[c] H, N, Cl	0.72
10	2	cis	Piperidyl	229–330.5	Et_2O–EtOH	$C_{17}H_{32}N_2 \cdot 2HCl \cdot 0.67H_2O$	C, H, N, Cl	0.4
11	1	cis	Piperidyl	264–265.5	Et_2O–EtOH	$C_{16}H_{30}N_2 \cdot 2HCl$	C, H, N, Cl	0.11
12	2	cis	NHC_6H_4OH-*p*	262–263	EtOH	$C_{18}H_{28}N_2O \cdot 2HBr$	C, H,[d] N, Br	<0.25
13	2	cis	$NHC_6H_4OCH_3$-*p*	241–243	EtOH	$C_{19}H_{30}N_2O \cdot 2HCl \cdot 0.5C_2H_6O$	C, H, N, Cl	1.1

[a] Activity in rat: tolbutamide = 1. [b] N: calcd, 8.58; found, 8.15. [c] C: calcd, 61.49; found 61.04. [d] H: calcd, 6.73; found 7.16.

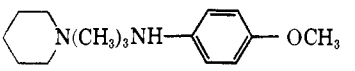
yields. Reduction of **6a** with LAH yielded the isoindoline **7a**. Cleavage of the phthalimide **6a** with hydrazine hydrate followed by hydrolysis with HCl afforded the primary amine **8a**.

Compds **9**, **10**, **11**, **13**, and **15** were prepared by the LAH reduction of the appropriate amides.[3] The preparations of **12** and **14** are described in the Experimental Section.

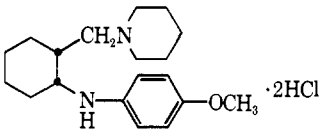
Biological Testing.—Glucose-primed, fasted (18–24 hr), Upjohn Sprague–Dawley, pathogen-free, male rats were the test animals. The test compd was administered orally at various dosages in 0.5 ml of sterile vehicle (6 rats/group). Immediately following administration of the test material, the animals were injected sc with 125 mg of glucose in 1 ml of 0.9% saline. Two hours later the rats were bled, *via* the vena cava, while under Cyclopal anesthesia, and blood glucose concns were determined by Technicon Auto-Analyzer, which utilizes a modification of a method described by Hoffman.[4] The relative activity of the test compd to that of tolbutamide is recorded in Table I.

Structure–Activity Relationship Considerations.—Compd **14**, which is closely related to the initial lead (**13**) but with the cyclohexane ring deleted, showed no activity. The compd (**15**) in which the relative positions of the *p*-anisidino and the piperidino groups were changed possessed no activity. Removal of the Me group (**12**) or removal of the entire aromatic nucleus (**8**) either eliminated or drastically reduced activity.

All active compds (in the series studied) possessed a secondary or tertiary aminomethyl N. The nature of the amine substituent could be varied considerably since alkyl, cyclic alkyl, aralkyl, and aryl groups afforded similar activity. The specific stereochemistry in one pair of isomers was not critical as both the cis (**4a**) and trans isomers (**4b**) possessed comparable activity.



14



15

Experimental Section[5]

Ethyl and Methyl *cis*-2-Piperidinocyclohexanecarboxylates (1a).—A mixt of Et and Me 2-cyclohexanonecarboxylates[6] (82 g, *ca.* 0.50 mole), piperidine (63.7 g, 0.75 mole), C_6H_6 (500 ml), and TsOH (0.5 g) was heated at reflux with a H_2O separator for 3 days. The solvent and excess piperidine were removed on a rotary evaporator, and the residue was vacuum distd to afford 76 g of material (enamine) boiling at 67–97° (0.05 mm). This material was dissolved in abs EtOH (200 ml) and hydrogenated for 24 hr in the presence of PtO_2 (0.5 g) at an initial pressure of 3.5 kg/cm². The catalyst was removed by filtration, and the solvent was removed on a rotary evaporator. The residue was dissolved in Et_2O (1 l.) and extd with dil HCl (3 × 20 ml). The combined exts were made strongly alk with NaOH and

(3) R. H. Rynbrandt and F. L. Schmidt, *J. Med. Chem.*, **14**, 54 (1971).

(4) W. S. Hoffman, *J. Biol. Chem.*, **120**, 51 (1937).

(5) All melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. The structures of all compds were supported by ir and nmr spectra and, in many cases, by mass spectra. Ir spectra were obtained on a Perkin-Elmer Model 421 recording spectrometer in Nujol mulls, the nmr spectra were recorded on a Varian A-60A spectrometer, and the mass spectra were determined on an Atlas CH-4 spectrometer. Where anal. are indicated only by symbols of the elements, anal. results obtained for these elements were within ±0.4% of the theor values.

(6) Aldrich Chemical Company, Inc., Milwaukee, Wis.

extd with Et_2O (3 × 20 ml). The combined exts were dried ($MgSO_4$), and the solvent was removed on a rotary evaporator. The residue was distd to afford 40.5 g (36% yield) of **1a**, bp 97–99° (0.02 mm).

Ethyl *trans*-2-Piperidinocyclohexanecarboxylate and ·HCl (1b).—A soln of **1a** (65 g, *ca.* 0.27 mole) in EtOH (50 ml) was added to a soln of Na (1 g) dissolved in abs EtOH (300 ml) and heated at reflux for 6 hr. The bulk of the solvent was removed on a rotary evaporator, and the residue was dissolved in H_2O (500 ml) and extd with Et_2O (3 × 150 ml). The Et_2O soln was treated as above to afford 27.5 g (42% yield) of **1b**, bp 87–90° (0.02 mm). A portion of this material was treated with Et_2O–HCl and ecrystd from EtOH–Et_2O, mp 121–122.5°. *Anal.* ($C_{14}H_{26}ClNO_2$) C, H, N.

***cis*-2-Piperidinocyclohexanemethanol and ·HCl (2a).**—A soln of **1a** (36 g, *ca.* 0.15 mole) in Et_2O (60 ml) was added dropwise to a cooled (<10°), stirred suspension of LAH (6 g, 0.15 mole) in Et_2O (300 ml). The mixt was stirred for an addnl 30 min at ice-bath temp and then heated at reflux for 30 min. The soln was cooled and treated dropwise with (1) H_2O (12 ml), (2) 20% aq Na_2CO_3 (4.5 ml), and (3) H_2O (22 ml). The ppt was removed by filtration and washed with Et_2O. The combined org solns were washed with H_2O (50 ml) and dried ($MgSO_4$). The solvent was removed on a rotary evaporator, and the residue was vacuum distd to give 26 g (88% yield) of **2a**, bp 100–102° (0.1 mm). A portion of this material was treated with Et_2O–HCl and recrystd from abs EtOH, mp 243–245°. *Anal.* ($C_{12}H_{24}ClNO$) C, H, N.

***trans*-2-Piperidinocyclohexanemethanol and ·HCl (2b).**—Redn of **1b** in a manner analogous to the cis isomer afforded the alcohol **2b**, bp 98–100° (0.02 mm). A portion of this material was treated with Et_2O–HCl and recrystd from Et_2O–EtOH, mp 192–195°. *Anal.* ($C_{12}H_{24}ClNO$) C, N, Cl, H: calcd, 9.93; found, 10.41.

***cis*-1[2-(Chloromethyl)cyclohexyl]piperidine·HCl (3a).**—A soln of **2a** (18.9 g, 0.096 mole) in $CHCl_3$ (60 ml) was added dropwise to a stirred, cooled (<10°) soln of $SOCl_2$ (14.3 g, 0.12 mole) in $CHCl_3$ (50 ml). The soln was stirred an addnl 45 min at ice-bath temp, 30 min at room temp and then heated at reflux for 1 hr. The bulk of the solvent and excess $SOCl_2$ were removed on a rotary evaporator, and the residue was recrystd from EtOH–Et_2O to give 24 g (98% yield) of **3a**, mp 201–203°. *Anal.* ($C_{12}H_{23}Cl_2N$) C, H, N.

***trans*-1-[2(Chloromethyl)cyclohexyl]piperidine·HCl (3b).**—Treatment of **2b** in a manner analogous to the cis isomer afforded **3b**, mp 191.5–192.5°. *Anal.* ($C_{12}H_{23}Cl_2N$) C, H, N.

1-[2-(Substituted-aminomethyl)cyclohexyl]piperidines (4a–5a).—An aq soln of **3a** or **3b** (5.0 g, 0.020 mole) was made alk with NaOH and extd with Et_2O (3 × 100 ml). The combined exts were dried ($MgSO_4$), and the solvent was removed on a rotary evaporator. The residue was mixed with the appropriate amine (0.040 mole), K_2CO_3 (5.52 g, 0.040 mole), and PhMe (12 ml) and heated at reflux with stirring for 20 hr. The mixt was cooled and the org layer was sepd and dried ($MgSO_4$). The solvent was removed on a rotary evaporator, and the residue was partially vacuum distd to remove excess $PhNH_2$ (100° bath at 0.1 mm). The pot residue was converted into the dihydrochloride with Et_2O–HCl and the product was recrystd (Table I).

***cis*- and *trans*-*N*-[(2-Piperidinocyclohexyl)methyl]phthalimide (6a and 6b).**—The free bases of **3a** and **3b** were prepd in the usual manner (see prepn of **4a**). A stirred mixt of the appropriate free base (0.020 mole), potassium phthalimide (4.1 g, 0.022 mole), and DMF (20 ml) was heated at 70–75° for 6 hr. The cooled mixt was dild with H_2O (150 ml) and extd with CH_2Cl_2 (3 × 100 ml). The combined exts were washed with dil NaOH (100 ml) and H_2O (100 ml) and dried ($MgSO_4$). The solvent was removed on a rotary evaporator, and the residue was recrystd (Table I).

***cis*-2-[(2-Piperidinocyclohexyl)methyl]isoindoline·2HCl (7a).**—Compd **6b** (2.0 g, 0.0061 mole) was added portionwise to a stirred, cooled (<10°) slurry of LAH (0.92 g, 0.0244 mole) in Et_2O (200 ml). After stirring for 2 hr in an ice bath, the sol was refluxed for 14 hr. The cooled mixt was treated dropwise with H_2O (2 ml), and the ppt was removed by filtration. The filtrate was dried ($MgSO_4$) and added dropwise to Et_2O–HCl. The ppt was removed and recrystd to afford 1.7 g (75% yield) of **7a** (Table I).

***cis*-1-[2-(Aminomethyl)cyclohexyl]piperidine·2HCl (8a).**—A mixt of **6a** (2.0 g, 0.0061 mole), $NH_2NH_2·H_2O$ (0.31 g, 0.0061 mole), and abs EtOH (30 ml) was heated at reflux for 3 hr. The cooled soln was treated with HCl (10 ml) and H_2O (30 ml) and heated at reflux for an addnl hr. The mixt was cooled, dild with H_2O (100 ml), and filtered. The filtrate was washed with Et_2O (2 × 75 ml), and the washings were discarded. The aq soln was made alk with NaOH and extd with Et_2O (3 × 100 ml). The combined exts were washed with H_2O (100 ml) and dried ($MgSO_4$). Et_2O–HCl was added, and the ppt was recrystd to afford 1.5 g (88% yield) of **8a** (Table I).

LAH Reduction of Amides—Compds **4a**, **4b**, **9–11**, **13**, and **15** were prepd by the LAH red of the appropriate amides.[3] The following prepn of **15** is a typical procedure. A soln of *cis*-1-[(2-*p*-anisidinocyclohexyl)carbonyl]piperidine (8.0 g, 0.023 mole) in Et_2O (175 ml) was added dropwise to a cooled suspension of LAH (3.3 g, 0.087 mole) in Et_2O (300 ml). The mixt was heated at reflux with stirring for 24 hr, cooled, and treated dropwise with (1) H_2O (7 ml), (2) 20% Na_2CO_3 soln (2.5 ml), and (3) H_2O (12 ml). The ppt was removed by filtration and washed with Et_2O (2 × 200 ml). The combined org portions were washed with H_2O (50 ml) and dried ($MgSO_4$). The solvent was removed on a rotary evaporator, and the residue was converted into the dihydrochloride with Et_2O–HCl and recrystd to afford 5.1 g (59% yield) of **15**, mp 240–241° (EtOH). *Anal.* ($C_{19}H_{32}Cl_2N_2O$) C, H, N, Cl.

***cis*-*p*-{[(2-Piperidinocyclohexyl)methyl]amino}phenol·2HBr (12).**—A soln of **13** (1.5 g, 0.0039 mole) in 48% HBr (35 ml) was heated at reflux for 20 hr. The soln was cooled, and the ppt was removed by filtration and washed with Et_2O. Recrystn afforded 1.2 g (69% yield) of **12** (Table I).

1-(3-*p*-Anisidinopropyl)piperidine·HCl (14).—A mixt of 1-(3-chloropropyl)piperidine[7] (32.2 g, 0.20 mole), *p*-anisidine (49.2 g, 0.40 mole), K_2CO_3 (55 g, 0.40 mole), and PhMe (100 ml) was heated at reflux for 19 hr. The cooled soln was treated with NaOH soln, and the org layer was sepd. The aq layer was extd with Et_2O (3 × 100 ml), and the combined org portions were dried ($MgSO_4$). The solvent was removed on a rotary evaporator, and the residue was vacuum distd to afford 21 g (42% yield) of product, bp 127–131° (0.1 mm). The dihydrochloride was prepd with Et_2O–HCl and recrystd to afford **14**, mp 236–237.5° (EtOH–Et_2O). *Anal.* ($C_{15}H_{26}Cl_2N_2O$) C, H, Cl.

Acknowledgment.—The authors are indebted to Dr. M. Grostic and Mr. R. J. Wnuk for mass spectra, Mr. P. A. Meulman for infrared spectra, and Mr. N. H. Knight and his associates for analytical data.

(7) R. R. Adams and F. C. Whitmore, *J. Amer. Chem. Soc.*, **67**, 736 (1945).