III or IV) the salt was collected and washed with Me_2CO. Some salts which gave incorrect analyses were dissolved in H_2O (*ca.* 150 ml/g) and treated with dil NH_4OH to pH 7 to ppt the base.

2-Imidazolylthiomethyl 2-Pyridyl Ketone·HBr.—2-(ω-Bromoacetyl)pyridine·HBr, prepd from 2-acetylpyridine (0.02 mole),[16] was treated with $NaHCO_3$ soln. An Et_2O ext of the base was washed (H_2O), dried ($MgSO_4$), and added to a soln of 2-mercaptoimidazoline (0.02 mole) in Me_2CO (300 ml). The Et_2O was evapd and the product filtered off (Table IV).

The corresponding 3- and 4-pyridyl ketones were obtained similarly starting with hydrobromides of 3-bromoacetylpyridine[17] and 4-bromoacetylpyridine.[18]

3-Substituted-5,6-dihydroimidazo[2,1-*b*]thiazoles (Tables V and VI). a.—The halomethyl ketone (0.01 mole), 2-mercaptoimidazoline (0.01 mole), and EtOH (10 ml) were heated under reflux for 2 hr. Usually a ppt formed rapidly than gradually dissolved and the hydrohalide crystd on cooling (variations to this procedure are indicated in Tables V and VI).

b.—The intermediate 2-phenacylthioimidazolinium salt or related compd (0.01 mole) and AcOH (10 ml) were heated under reflux for 16 hr and the soln was evapd. The salt was either recrystd or treated with aq $NaHCO_3$, and the base was extd with EtOAc. The EtOAc was washed (H_2O), dried ($MgSO_4$), and evapd, and the residue was recrystd.

3-(4-Pyridyl)-5,6-dihydroimidazo[2,1-*b*]thiazole·2HBr.—2-Imidazolylthiomethyl 4-pyridyl ketone·HBr and a mixt of AcOH and 48% HBr (1:1) were heated under reflux for 4 hr. The soln was evapd and the residue was recrystd.

***N*-Acetyl-2-phenacylthioimidazoline.**—2-Phenacylthioimidazoline (0.6 g), THF (10 ml), and Ac_2O (0.3 ml) were stirred 16 hr. The soln was evapd and the residue was partitioned between aq $NaHCO_3$ and EtOAc (*ca.* 150 ml). The EtOAc was washed (H_2O), dried ($MgSO_4$), and cond to give 0.45 g, mp 149.0–149.5°, ν_{max} 1670 cm^{-1}. *Anal.* ($C_{13}H_{14}N_2O_2S$) C, H, N.

2-(3,4-Dichlorophenoxymethyl)imidazolinium Chloride.—Treatment of 3,4-dichlorophenol with chloracetonitrile[19] and purification of the crude product by chromatog on alumina with C_6H_6 gave 73% 3,4-dichlorophenoxyacetonitrile, mp 63–64° (petr ether, 80–100°). *Anal.* ($C_8H_6Cl_2NO$) C, H, N. Treatment of the product with ethylenediamine tosylate by the general method[19] gave the imidazoline, isolated as the hydrochloride in 45% yield, mp 243–244° (*i*-PrOH). *Anal.* ($C_9H_{11}Cl_2N_2O$) C, H, N.

(16) G. R. Clemo, W. McG. Morgand, and R. Raper, *J. Chem. Soc.*, 965 (1937).

(17) H. McKennis, Jr., L. B. Turnbull, E. R. Bowman, and E. Tamaki, *J. Org. Chem.*, **28**, 383 (1963).

(18) L. Polo Friz, *Farmaco Ed. Sci.*, **18**, 972 (1963).

(19) W. B. Neely, H. C. White, and A. Rudzik, *J. Pharm. Sci.*, **57**, 1176 (1968).

Chemistry and Pharmacology of 5-Methylene-4-substituted Dibenzo[*a*,*d*]cycloheptenes

LESLIE G. HUMBER,*

Department of Chemistry

FERENC HERR, AND MARIE-PAUL CHAREST

Department of Pharmacology, Ayerst Research Laboratories, Montreal, Quebec, Canada

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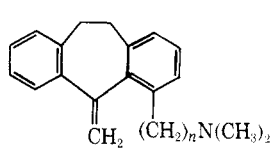
Methods are described, utilizing the Hofmann degradation of *N*,*N*-dimethyl-1,2,3,7,8,12b-hexahydrobenzo[6,7]cyclohepta[1,2,3-*d*,*e*]isoquinolinium hydroxide, which allow the synthesis of 5-methylene-10,11-dihydro-5*H*-dibenzo[*a*,*d*]cycloheptenes bearing basic side chains, of varying lengths, at the 4 position. The lack of antidepressant activity in these compds shows that the presence of a C_5–$C_{1'}$ trigonal center, and of a basic side chain attached to the 4 position are insufficient for retention of amitriptyline-like activity.

This work stems from our wish to examine the hypothesis that the C_5–C_1' trigonal center, and the basic center of the antidepressant amitriptyline, **1**, need not be joined through a 2-C alkylene chain. More particularly, in molecules of type **2**, in which the basic center is attached to position 4 of the dibenzo[*a*,*d*]-cycloheptene nucleus through alkylene chains of various lengths from $n = 1$ to $n = 3$, examination of molecular models shows that conformations exist in which the positions that can be assumed by the basic center relative to the nucleus, can, in turn, coincide with virtually all of those which are permissible for amitriptyline. These features of the molecules of type **2**, along with the retention of an exocyclic double bond at C-5, make them attractive candidates for pharmacological investigation.

1



2

Chemical methods have thus been developed allowing the syntheses of the compds **2** with $n = 1, 2, 3$. Intermediates available have permitted the preparation of desmethyl, and of 5,1′-dihydro derivatives, and compounds of these types have also been made for pharmacological examination.

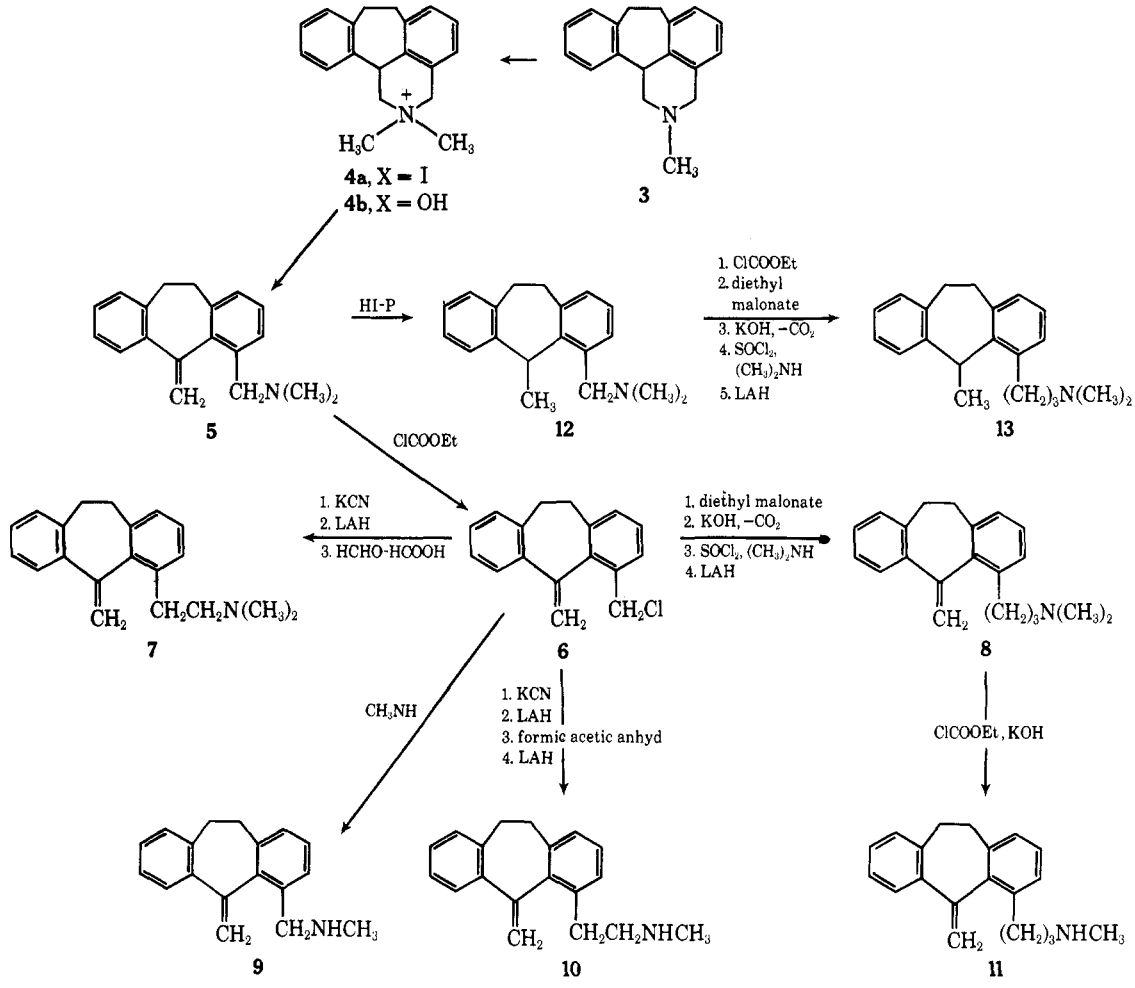
Chemistry.—Recent work from this laboratory[1] has made available *N*-methyl-1,2,3,7,8,12b-hexahydrobenzo[6,7]cyclohepta[1,2,3-*d*,*e*]isoquinoline, **3**. The corresponding methohydroxide **4b**, prepared from the methiodide **4a** by ion-exchange chromatog, undergoes an extraordinarily facile Hofmann degradation in high yield to afford the 5-methylene-4-methyldimethylamine (**5**), one of the desired final products.

The Gadamer–Knoch[2] modification of the von Braun degradation, using ethyl chloroformate instead of BrCN, when applied to **5** proceeds with exclusive cleavage between the N and the benzylic C to give the benzyl chloride **6**. This key intermediate, **6**, has been transformed by conventional series of reactions into desired final products **7** (**14**, **15**), **8** (**17**, **18**, **19**), **9**, **10** (**14**, **15**, **16**), and **11**. The required 5,1′-dihydro derivative **12** was obtained by reduction of **5**, in high yield

(1) L. G. Humber, M. A. Davis, R. A. Thomas, R. Otson, and J. R. Watson, *J. Heterocycl. Chem.*, **3**, 247 (1966).

(2) J. Gadamer and F. Knoch, *Arch. Pharm. (Weinheim)*, **259**, 135 (1921).

SCHEME I



with HI and red P, while a conventional series of reactions on **12** affords the dihydro derivative **13** (**20**, **21**, **22**). The numbers in parentheses refer to intermediates whose formulas do not appear in Scheme I, but which are described in the Experimental Section.

Pharmacology.—All compounds were tested in mice and some in rats for biological properties, especially for effects on the CNS. They were compared with amitriptyline for antidepressant-like activities. The biological data are summarized in Table I. The LD_{50} in mice was approximated by giving increasing doses of the compounds ip to only 5 animals per dose. For this reason standard errors were not calculated. During the determination of toxicity, behavioral observations were made using a scoring system for 20 parameters. Symptomalogy was also scored at a dose of 0.25 of the LD_{50}. Narcosis potentiation was measured by determining the dose of the compound which caused the mice to lose their righting reflex after a subnarcotic dose of ethanol.[3] ED_{50}'s are also shown in the antireserpine test.[4] In this test the prevention of ptosis caused by 4 mg/kg of reserpine was measured.

TABLE I

PHARMACOLOGICAL ACTIVITIES IN MICE[a]

Compd	Approximate LD_{50}	Narcosis potentiation ED_{50}	Antireserpine ED_{50}
5	90	8.4 ± 2	>40
7	135	39.2 ± 3	41.6 ± 6
8	90	12 ± 2	>25
9	45	>30	>12
11	110	21.7 ± 0.4	32 ± 4
15	135	17.4 ± 2	>40
12	110	25.7 ± 2	>40
13	150	>40	
Amitriptyline	94 ± 3	7.2 ± 0.7	22 ± 3

[a] The compds were administered ip. The results are expressed as ED_{50} in mg/kg ± standard error.

From the results, it can be seen that most of the new compounds have narcosis-potentiating effects indicating some CNS activity. The most potent was **5** with an ED_{50} of 8.4 mg/kg. From the antireserpine test and the behavioral observations in mice it can be concluded that the new derivatives do not have amitriptyline-like antidepressant effects.[5] Similarly no behavioral stimulant or depressant effects were seen in 0.25 of the LD_{50}. A few compounds were evaluated in the antitetrabenazine test in rats with results similar to those found in the antireserpine test.

Further tests to which the compounds were submitted were (1) effect on electroshock seizures, (2) antipentylenetetrazole activity, (3) ataxic effect by the rotarod method, and (4) analgetic activity by the radiant heat method. In none of these tests did the

(3) F. Herr, J. Stewart, and M.-P. Charest, *Arch. Int. Pharmacodyn.*, **134**, 328 (1961).

(4) B. Rubin, M. H. Malone, M. H. Waugh, and J. C. Burke, *J. Pharmacol. Exp. Ther.*, **120**, 125 (1957).

(5) J. Stewart, M.-P. Charest, and F. Herr, *J. Med. Chem.*, **6**, 338 (1963).

compounds show properties which would indicate any specific CNS or peripheral effect.

Conclusion.—The inactivity of these compounds in the antireserpine test answers the question posed in the introduction, in that the structural features of compounds of type **2** are clearly insufficient for antidepressant activity, and suggests that a definition of the essential structural features required for such activity cannot be made in terms of the structural parameters and rotational freedoms considered in this work.

Experimental Section

Melting points were determined on a Thomas-Hoover apparatus and are corrected. Analyses were done by Mr. W. Turnbull and staff of our laboratories, and, where indicated only by symbols of the elements, the results are within ±0.4% of the calcd values. Nmr analyses were carried out on an Varian A-60A nmr spectrometer and are reported in δ (ppm) calibrated against TMS.

2,2-Dimethyl-1,2,3,7,8,12b-hexahydrobenzo[6,7]cyclohepta-[1,2,3-*d,e*]isoquinolinium Iodide (4a).—2-Methyl-1,2,3,7,8,12b-hexahydrobenzo[6,7]cyclohepta[1,2,3-*d,e*]isoquinoline (**3**) was treated with MeI in Me_2CO at 22°. The product, formed in 85% yield, was crystd from MeCN and retained 1 mole of solvent. It had mp 208°, $\lambda_{max}^{CHCl_3}$ 2250 cm (C≡N). *Anal.* ($C_{19}H_{22}IN \cdot CH_3CN$) C, H, I, N.

10,11-Dihydro-*N,N*-dimethyl-5-methylene-5*H*-dibenzo[*a,d*]-cycloheptene-4-methylamine (5).—An ion-exchange column was prepd from 4.0 g of dry Dowex-2-X8 (capacity, 3.1 mequiv/g) and converted to the OH^- form by filtering 60 ml of 1 *N* NaOH through it. The column was washed to pH 7 with H_2O and then with 2:1 H_2O–MeOH. The quaternary methiodide **4a** (1.0 g) was dissolved in 30 ml of MeOH and 20 ml of H_2O was added. This soln was passed through the column and then it was washed with 2:1 H_2O–MeOH to pH 7. The solvents were evapd *in vacuo*. The remaining oil was dissolved in C_6H_6 and a small amt of insol material was removed. Removal of the C_6H_6 and crystn of the residue from MeCN gave the product in 90% yield, mp 62°, nmr ($CDCl_3$) δ 5.23 (d, 1, *J* = 1.5 Hz, H-1′), 5.70 (d, 1, *J* = 1.5 Hz, H-1′), 2.21 (s, 6, H's of $N(CH_3)_2$). *Anal.* ($C_{19}H_{21}N$) C, H, N. The HCl salt had mp 229° (MeCN). *Anal.* ($C_{19}H_{22}ClN$) C, H, N, Cl.

10,11-Dihydro-5-methylene-5*H*-dibenzo[*a,d*]cycloheptene-4-methyl Chloride (6).—Ethyl chloroformate (3.16 g, 0.03 mole) in C_6H_6 (10 ml) was added during 10 min to a refluxing soln of **5** (5.2 g, 0.02 mole) in C_6H_6 (50 ml). After 90 min the solvent was evpd *in vacuo* to afford the product, 4.2 g (79%), mp 115° (MeCN). *Anal.* ($C_{17}H_{15}Cl$) C, H, Cl.

10,11-Dihydro-*N*-methyl-5-methylene-5*H*-dibenzo[*a,d*]cycloheptene-4-methylamine (9).—Anhyd $MeNH_2$ (40 ml), EtOH (80 ml), and **6** (10.0 g) were heated in a pressure bottle for 16 hr at 65°. A conventional work-up afforded the product as an oil (45%). The HCl salt had mp 170° (MeCN). *Anal.* ($C_{18}H_{20}ClN$) C, H, Cl.

10,11-Dihydro-5-methylene-5*H*-dibenzo[*a,d*]cycloheptene-4-acetonitrile (14).—A mixt of KCN (1.0 g), DMF (20 ml), H_2O (2 ml), and **6** was heated at 100° for 3 hr. The usual work-up procedure gave an oil which was passed through a column of alumina (activity II) with C_6H_6 as eluant. Crystn from hexane gave the product, mp 110°, 0.9 g (90%). *Anal.* ($C_{18}H_{15}N$) C, H, N.

2′-(10,11-Dihydro-5-methylene-5*H*-dibenzo[*a,d*]cycloheptene-4)-ethylamine (15).—To a mixt of $AlCl_3$ (12.3 g) and LAH (3.4 g) in Et_2O (220 ml) was added a soln of **14** in Et_2O (510 ml). The mixt was refluxed for 3 hr and then H_2O (2 l.) was added. The soln was made alkaline with 4 *N* NaOH and the ether phase was dried and fractionally distd to afford 17 g of the product (86%), bp 142–146° (0.1 mm). The maleate salt had mp 180° (*i*-PrOH). *Anal.* ($C_{22}H_{23}NO_4$) C, H, N.

***N*-Formyl-2′-(10,11-dihydro-5-methylene-5*H*-dibenzo[*a,d*]-cycloheptene-4)-ethylamine (16).**—To formic acetic anhydride (prepd by heating 98% HCOOH (5.1 ml) and Ac_2O (12.1 g) at 58° for 2 hr) was added **15** at 0°. The stirred mixt was kept at 22° for 16 hr and poured into iced H_2O. The $CHCl_3$ ext was washed with $NaHCO_3$ soln to afford the product as an oil (7.0 g, 90%), bp 210° (0.1 mm). *Anal.* ($C_{19}H_{19}NO$) C, H, N.

***N*-Methyl-2′-(10,11-dihydro-5-methylene-5*H*-dibenzo[*a,d*]-cycloheptene-4)-ethylamine (10).**—Compd **16** (6.0 g) was reduced with LAH (1.2 g) by refluxing in THF (300 ml) for 5 hr. The usual work-up procedure afforded the product as an oil (6.0 g). The maleate salt had mp 146° (Me_2CO). *Anal.* ($C_{23}H_{25}NO_4$) C, H, N.

***N,N*-Dimethyl-2′-(10,11-dihydro-5-methylene-5*H*-dibenzo-[*a,d*]cycloheptene-4)-ethylamine (7).**—Compd **15** (5.0 g) was heated for 16 hr at 100° with a mixt of HCOOH (5.0 ml), H_2O (5.0 ml), and 37% HCHO (5 ml). The usual work-up procedure gave the product as an oil. The maleate salt (5.7 g) was obtained cryst from *i*-PrOH and had mp 156°. *Anal.* ($C_{24}H_{27}NO_4$) C, H, N.

Diethyl (10,11-Dihydro-5-methylene-5*H*-dibenzo[*a,d*]cycloheptene-4)-methylenemalonate (17).—To diethyl sodiomalonate (prepd from Na (0.23 g), and diethyl malonate (1.6 g) in EtOH (20 ml)) was added **6** (2.5 g). The mixt was refluxed for 2 hr then worked up in the usual manner to afford a quant yield of the product as an oil. An anal. sample had bp 180° (0.01 mm). *Anal.* ($C_{24}H_{26}O_4$) C, H.

3′-(10,11-Dihydro-5-methylene-5*H*-dibenzo[*a,d*]cycloheptene-4)-propionic Acid (18).—Compd **17** (3.78 g) was refluxed in EtOH (20 ml) for 2 hr with 85% KOH (1.3 g). The usual work-up procedure afforded the malonic acid which was decarboxylated by heating at 150° for 1.5 hr at 0.01 mm. The product was obtd in 71% yield and had mp 178° (C_6H_6). *Anal.* ($C_{19}H_{18}O_2$) C, H.

***N,N*-Dimethyl-3′-(10,11-dihydro-5-methylene-5*H*-dibenzo-[*a,d*]cycloheptene-4)-propionamide (19).**—To a mixt of $Me_2NH \cdot HCl$ (16.0 g) in H_2O (150 ml) and C_6H_6 (100 ml) was added simultaneously 500 ml of 0.5 *N* NaOH and 100 ml of a C_6H_6 soln of 15 g of the acid chloride of **18** (prepd from **18** with $SOCl_2$ and DMF). The C_6H_6 phase gave the crude product which was chromatogd on silica gel. Elution with EtOAc afforded the pure product in 90% yield, mp 111–113° (isooctane–EtOAc). *Anal.* ($C_{21}H_{23}NO$) C, H, N.

***N,N*-Dimethyl-3′-(10,11-dihydro-5-methylene-5*H*-dibenzo-[*a,d*]cycloheptene-4)propylamine (8).**—Compd **19** (1.0 g) was reduced with LAH (1.0 g) in THF (50 ml) by refluxing for 3 hr. The usual work-up procedure afforded the product (0.9 g, 89%) as an oil. The HCl salt had mp 124° (*i*-PrOH–Et_2O), nmr ($CDCl_3$) δ 2.52 (s, 6, H's of N (CH_3)$_2$), 5.20 (d, 1, *J* = 1.5 Hz, H-1′), 5.70 (d, 1, *J* = 1.5 Hz, H-1′). *Anal.* ($C_{21}H_{26}ClN$) Cl, N.

***N*-Methyl-3′-(10,11-dihydro-5-methylene-5*H*-dibenzo[*a,d*]-cycloheptene-4)-propylamine (11).**—Compd **8** (4.5 g) was refluxed in C_6H_6 (45 ml) with ethyl chloroformate (6.0 g) for 2 hr. The cooled soln was washed with 3% aq HCl to afford the crude *N*-carboethoxy derivative (3.6 g), $\nu_{max}^{CHCl_3}$ 1680 cm^{-1}. It was refluxed for 16 hr with 85% KOH (0.9 g) in propylene glycol (14 ml), then H_2O (50 ml) was added, and the mixt was extd with C_6H_6. The C_6H_6 phase was extd with 5% aq HCl, and the acidic ext was made basic with NaOH soln and extd with $CHCl_3$ to afford the product (1.5 g) as an oil. The HCl salt had mp 162–164° (MeCN). *Anal.* ($C_{20}H_{24}ClN$) C, H, Cl, N.

10,11-Dihydro-*N,N*,5-trimethyl-5*H*-dibenzo[*a,d*]cycloheptene-4-methylamine (12).—A mixt of **5** (90 g), AcOH (900 ml), 57% HI (450 ml), and red P (90 g) was refluxed for 16 hr. A conventional work-up procedure gave the product (85 g, 94%), mp 76–77° (EtOH), nmr ($CDCl_3$) δ 4.85 (q, 1, *J* = 7.5 Hz, H-5), 1.63 (d, 3, *J* = 7.5 Hz, H-1′). *Anal.* ($C_{19}H_{23}N$) C, N, N. The HCl salt had mp 205–207° (EtOH). *Anal.* ($C_{19}H_{24}ClN$) C, H, N, Cl. This compd has also been prepared, less conveniently, by hydrogenation of **5** with PtO_2 in AcOH at atm press for 16 hr.

10,11-Dihydro-5-methyl-5*H*-dibenzo[*a,d*]cycloheptene-4-methyl Chloride (20).—Treatment of **12** with ethyl chloroformate in C_6H_6 as described above for the prepn of **6**, afforded the product in 71% yield, mp 82–84° (hexane). *Anal.* ($C_{17}H_{17}Cl$) C, H, Cl.

3-(10,11-Dihydro-5-methylene-5*H*-dibenzo[*a,d*]cycloheptene-4)-propionic Acid (21).—Treatment of **20** with diethyl sodiomalonate, followed by hydrolysis and decarboxylation as described above for **17**, afforded the product in 86% yield, mp 149–151° (MeCN). *Anal.* ($C_{19}H_{20}O_2$) C, H. This compd has also been prepd less conveniently by hydrogenation of **17** with PtO_2 in AcOH at atm press for 16 hr.

3-(10,11-Dihydro-*N,N*,5-trimethyl-5*H*-dibenzo[*a,d*]cyclohep-tene-4)-propionamide (22).—This compd was prepd by treatment of the acid chloride of **21** with $Me_2NH \cdot HCl$ and NaOH as described in the prepn of **17**, above. The product was obtained in 88% yield and had mp 79–81° (hexane–EtOAc). *Anal.* ($C_{21}H_{23}NO$), C, H, N.

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

RONALD H. RYNBRANDT,* FREDERICKA L. SCHMIDT, AND JACOB SZMUSZKOVICZ

Research Laboratories, The Upjohn Company, Kalamazoo, Michigan 49001

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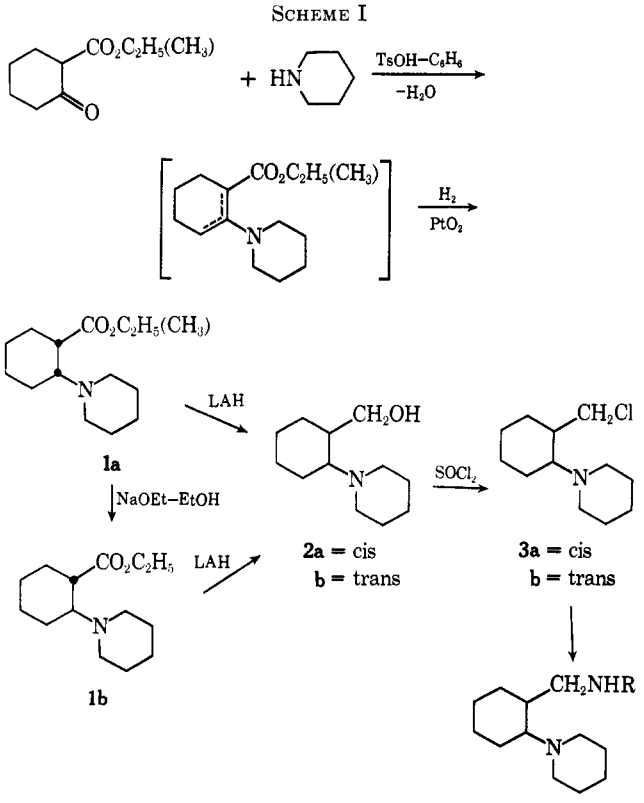
The synthesis and hypoglycemic activity of *cis*-1-[2-(*p*-anisidinomethyl)cyclohexyl]piperidine (**13**), a representative of a new class of hypoglycemic agents, are described. A structure–activity relationship study involving the preparation and hypoglycemic testing of 13 compounds related to **13**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

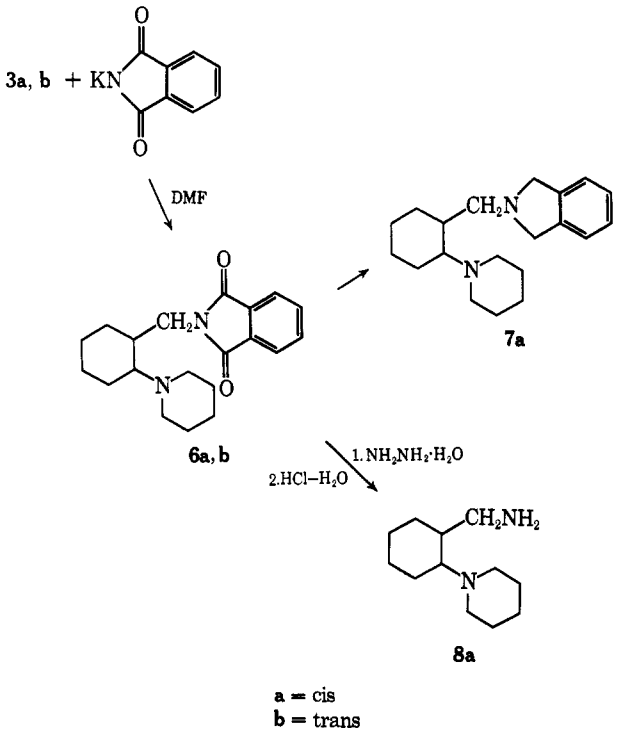
SCHEME I



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.