0.23 g of Na had been dissolved, was heated in an open Berzelius beaker at 130–140° for 16 hr. The solid, precipitating on cooling, was filtered off. The crude product (63.5 g) was dissolved in boiling EtOH (90%) and acidified with HCl and the slight precipitate that formed was filtered off. The solvent was removed and the residue was crystallized from cyclohexane; mp 98–100°, yield 45.0 g (48%). *Anal.* ($C_{13}H_{14}O_3$) C, H. Ir absorption bands were as expected.

Benzyl (o-Acetoxyphenyl)acetate (X).—A mixture of 24.2 g (0.1 mole) of VIII, 50 ml of Ac$_2$O, and 3 ml of pyridine (or 1.5 ml of H$_2$SO$_4$) was heated on a water bath for 2–3 hr. After pouring into ice water, the oily layer was separated and diluted (Et$_2$O). The ether solution was washed twice with saturated NaCl and dried (Na$_2$SO$_4$). Evaporation of the solvent and distillation of the residue gave 22.9 g (80%) of product: bp 168–172° (0.4 mm); $n^{26.5}$D 1.5425; d^{27}_4 1.132; FeCl$_3$ test (phenolic OH), negative. *Anal.* ($C_{17}H_{16}O_4$) C, H. Ir absorption bands were as expected.

o-Acetoxyphenylacetic Acid (I).—A solution of 22.9 g (0.0806 mole) of X in 100 ml of anhydrous MeOH was hydrogenated over 1 g of 5% Pd–C at room temperature at an initial pressure of 4.2 kg/cm^2 for 2 hr. Filtration of the catalyst followed by removal of the solvent *in vacuo* yielded a viscous oil which crystallized on refrigeration overnight; yield 13.0 g (83%). A sample recrystallized twice from C$_6$H$_6$–cyclohexane melted at 62–63°; λ$_{max}$ 5.68 (acetoxy C=O), 5.88 (carboxyl C=O), 8.10 (ester C–O–C), 3.2–3.45 μ (COOH). *Anal.* ($C_{10}H_{10}O_4$) C, H, neut equiv.

Pharmacological Data.—Carworth Farms male, CF-1 strain mice, weighing 13–18 g were dosed orally with the ED$_{50}$ dose of aspirin or an equivalent dose of the other compounds on a molecular weight basis. Control groups received 1% tragacanth, 10 ml/kg. Ten mice per group were used and six groups served as controls.

Twenty minutes after dosing, the animals were given a 0.2-ml ip injection of bradykinin (Sandoz) diluted to 100 μg/ml with triply distilled deionized H$_2$O. Fifteen minutes later the animals were reinjected with 0.1 ml and observed for writhing for a period of 20 min. The results are summarized in Table I.

Discussion

The biological data available here are somewhat puzzling. Bauer and Lasala[1] state that theoretically the most promising homologous series is the one in which the aspirin molecule is altered in the aliphatic acid side chain rather than in the acyl moiety. Their results with II apparently support this claim. In fact, their results with the D'Amour–Smith method appear to show a greater activity for II than for aspirin. The bradykinin-writhing method, however, fails to show any significant activity. It is also interesting that the vinylog IIIa shows no activity. Even though Bauer and Lasala[1] prepared this compound as an intermediate they did not test it and therefore a comparison of methods cannot be made. The *cis* isomer IIIb appears to have some activity, based on the limited screening tests reported here. Compound I proved quite inactive by the bradykinin method. The question now arises whether the two methods used for analgetic screening are equally useful, at least with aspirin analogs. Perhaps a reevaluation of the comparative results obtainable with these two methods for salicylate-type analgetics is needed.

2,6-Dialkylpiperazines. V.[1] Synthesis of 2,6-Alkylpiperazine Derivatives Structurally Related to Cinnarazine

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In the first paper of this series[3] a four-step synthesis of *cis*-2,6-dimethylpiperazine (Ia) was reported. We have now found that the procedure summarized in Chart I can be extended to the synthesis of different 2,6-substituted piperazines (I) starting from a given RR'C(NH$_2$)COOC$_2$H$_5$ (IIb and c) and N-benzyl-α-bromopropionamide (IIIa). 2-Isopropyl-6-methylpiperazine (Ib) and 2,2,6-trimethylpiperazine (Ic) were thus synthesized. The use of N-benzyl-α-bromoamides different from IIIa, used in the earlier synthesis of I, was unsuccessful in the two cases examined. N-Benzyl-α-bromoisovaleramide (IIIb) condensed with valine ethyl ester (IIb), but the corresponding ethyl ester benzylamide IVb when heated at 250–260° formed resinous material from which Vb was not isolated; N-benzyl-α-bromoisobutyramide (IIIc) failed to condense with ethyl α-aminoisobutyrate (IIc).

Availability of Ia–c prompted us to investigate the pharmacological properties of compounds in which the piperazine nucleus was replaced by these derivatives. 1-Cinnamyl-4-benzhydrylpiperazine (cinnarazine), active as an antihistaminic agent,[4] was chosen as model compound. We synthesized 1-cinnamyl-4-benzhydryl-2,6-substituted piperazines (VIIIa–c) through the pathway summarized in Chart I. Refluxing of Ia–c with an equimolar amount of benzhydryl chloride and triethylamine in toluene led to the 4-benzhydryl derivative (VIIa–c). The structure of VIIa–c was proved by an unambigous synthesis. Acylation of VIa with propionic anhydride gave 1-propionyl-4-benzyl-2,6-dimethylpiperazine (XIa) which was catalytically debenzylated to 1-propionyl-2,6-dimethylpiperazine (Xa). Condensation of Xa with benzhydryl chloride led to 1-propionyl-4-benzhydryl-2,6-dimethylpiperazine (XIa), which was found identical (mixture melting point and ir spectra) with the product obtained by propionylation of VIIa. Efforts to obtain VIIa by acid hydrolysis of XIa led to isolation of a mixture of starting compound and 1-propionyl derivate Xa, caused apparently by a preferential cleavage of the N-benzhydryl bond. Finally, condensation of VIIa–c with cinnamyl chloride in refluxing toluene and in the presence of an equimolar amount of triethylamine led to the desired compounds. We were also interested in synthesizing 1-benzhydryl-4-cinnamyl-2,6-substituted piperazines, isomers of VIIIa–c, in order to define the influence of the reversal of the substituents in the 1 and 4 position on the pharmacological activity. Any effort to introduce the bulky benzhydryl group in the N^1 position of the 2,6-substituted piperazine nucleus by treating benzhydryl halides

(1) Paper IV: G. Cignarella and E. Testa, *J. Med. Chem.*, **11**, 592 (1968).
(2) To whom inquiries should be addressed.
(3) G. Cignarella, *J. Med. Chem.*, **7**, 241 (1964).
(4) B. N. Halpern, C. Stiffel, M. Liacopoulos-Briot, and L. Conovici, *Arch. Intern. Pharmacodyn.*, **142**, 170 (1963).
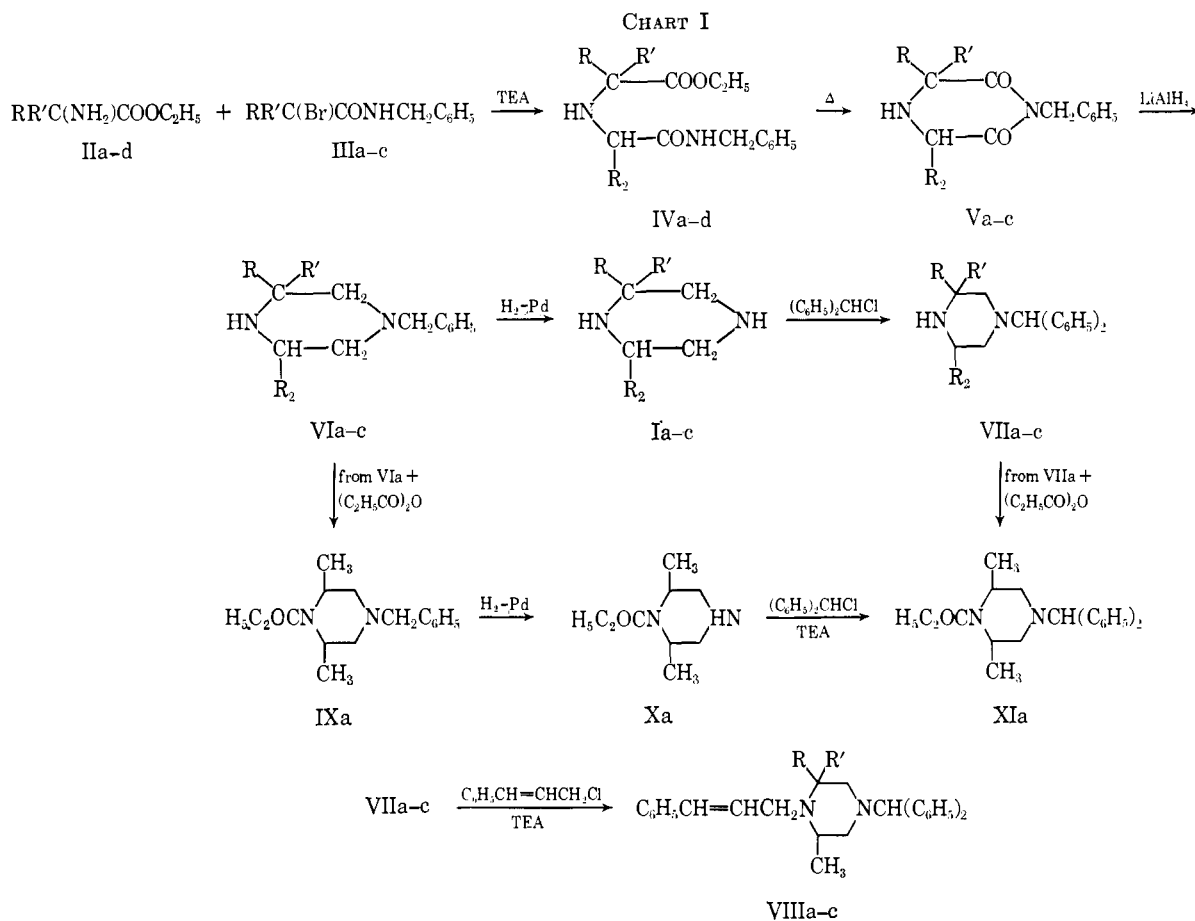
Chart I

$RR'C(NH_2)COOC_2H_5$ + $RR'C(Br)CONHCH_2C_6H_5$ $\xrightarrow{\text{TEA}}$

IIa–d   IIIa–c

IVa–d $\xrightarrow{\Delta}$ Va–c $\xrightarrow{\text{LiAlH}_4}$

VIa–c $\xrightarrow{\text{H}_2\text{–Pd}}$ Ia–c $\xrightarrow{(C_6H_5)_2CHCl}$ VIIa–c

from VIa + $(C_2H_5CO)_2O$

from VIIa + $(C_2H_5CO)_2O$

IXa $\xrightarrow{\text{H}_2\text{–Pd}}$ Xa $\xrightarrow[\text{TEA}]{(C_6H_5)_2CHCl}$ XIa

VIIa–c $\xrightarrow[\text{TEA}]{C_6H_5CH=CHCH_2Cl}$ VIIIa–c

a, R = R_2 = CH_3; R' = H
b, R = $CH(CH_3)_2$; R' = H; R_2 = CH_3
c, R = R' = R_2 = CH_3
d, R = H; R' = R_2 = $CH(CH_3)_2$

Table I

Compd	R	R'	R_2	Yield, %	Bp, °C (mm)	Formula	Analyses
IVb	H	$CH(CH_3)_2$	CH_3	74	180–185 (1)	$C_{17}H_{26}N_2O_3$	C, H, N
IVc	CH_3	CH_3	CH_3	58	160 (0.5)	$C_{16}H_{24}N_2O_3$	C, H, N
IVd	H	$CH(CH_3)_2$	$CH(CH_3)_2$	31, 8	150–152 (0.5)	$C_{19}H_{30}N_2O_3$	C, H, N

with VIa–c was unsuccessful probably because of the steric hindrance at N^1 due to the adjacent methyl groups.

Antihistaminic activity of the synthesized cinnarazine derivatives was measured *in vitro* on the isolated guinea pig ileum on the basis of antagonizing the contractile response elicited by histamine, added to the bath in a concentration of 0.1 μg/ml. The only compound sufficiently soluble to be tested (VIIIb) possessed a substantially lower antihistamine activity than cinnarazine itself.

Experimental Section[5]

Materials and Intermediates.—α-Alanine ethyl ester[6] (IIa), valine ethyl ester[7] (IIb), ethyl α-aminoisobutyrate[8] (IIc), N-

benzyl-α-bromopropionamide[3,9] (IIIa), N-benzyl-α-bromoisovaleramide[9] (IIIb), and N-benzyl-α-bromoisobutyramide[9] (IIIc) were prepared by known procedures. The synthesis of 2,2'-iminodipropionic ethyl ester benzylamide, bp 155–160° (0.5 mm) (IVa), 4-benzyl-2,6-dimethylpiperazine-3,5-dione (Va), 4-benzyl-2,6-dimethylpiperazine (VIa), and 2,6-dimethylpiperazine (Ia) has been reported in a preceding paper.[3]

General Directions for IVa–d.—An equimolecular solution of IIIa–c, IIa–d, and Et₃N in about 5 vol (with respect to III) of dry PhMe was refluxed for many hours with stirring. After cooling, $Et_3N \cdot HBr$ was filtered off and the solvent was evaporated under reduced pressure. The residue was suspended in 10% HCl and extracted with Et_2O. The acid solution was made alkaline with NaOH. The extract was dried (Na_2SO_4), the solvent was evaporated, and the oily residue was distilled. Compounds IVb–d obtained are listed in Table I.

2,6-Disubstituted 4-Benzylpiperazine-3,5-diones (Va–c, Table II). General Method.—The procedure has been described
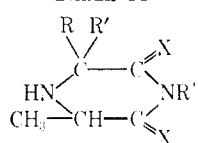
(5) Where analyses are indicated only by symbols of the elements or functions, analytical results obtained for those elements or functions were within ±0.4% of the theoretical values.

(6) R. W. Chambers and F. H. Carpenter, *J. Am. Chem. Soc.*, **77**, 1522 (1955).

(7) M. D. Slimmer, *Ber.*, **35**, 400 (1902).

(8) N. Zelinsky, A. Annenkow, and J. Kulikow, *Z. Physiol. Chem.*, **73**, 459 (1911).
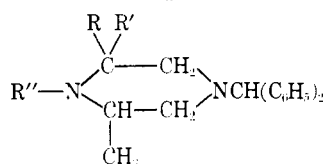
(9) C. A. Bischoff, *Ber.*, **31**, 3236 (1898).

TABLE II

R R'
\ /
C——C
/ \
HN   NR''
| /
CH₃—CH—C
\
X

Compd	X	R	R'	R''	Yield, %	Bp (mm) or mp, °C	Formula	Analyses
Va[3]	O	H	CH₃	CH₂C₆H₅	85	150-155 (0.6)	C₁₃H₁₆N₂O₂	C, H, N
					...	212-214 (EtOH)	C₁₃H₁₆N₂O₂·HCl	C, H, N, Cl
Vb	O	H	CH(CH₃)₂	CH₂C₆H₅	79	145-150 (0.6)	C₁₅H₂₀N₂O₂	C, H, N
Vc	O	CH₃	CH₃	CH₂C₆H₅	75	160 (0.8)	C₁₄H₁₈N₂O₂	C, H, N
					...	220-226 (EtOH-Et₂O)	C₁₄H₁₈N₂O₂·HCl	C, H, N, Cl
VIa[3]	H₂	H	CH₃	CH₂C₆H₅	95	85-86 (0.6)	C₁₃H₂₀N₂	C, H, N
VIb	H₂	H	CH(CH₃)₂	CH₂C₆H₅	85	100-102 (0.5)	C₁₅H₂₄N₂	C, H, N
VIc	H₂	CH₃	CH₃	CH₂C₆H₅	87	80-82 (0.6)	C₁₄H₂₂N₂	C, H, N
					...	212-215 (EtOH-Et₂O)	C₁₄H₂₂N₂·2HCl	C, H, N, Cl
Ia[3]	H₂	H	CH₃	H	84	140-154 (750)	C₆H₁₄N₂	C, H, N
Ib	H₂	H	CH(CH₃)₂	H	87	95-97 (22)	C₈H₁₈N₂	C, H, N
					...	300 (EtOH)	C₈H₁₈N₂·2HCl	C, H, N, Cl
					...	252-256 (EtOH)	C₈H₁₈N₂·2C₆H₃N₃O₇[a]	C, H, N
Ic	H₂	CH₃	CH₃	H	73	158-160 (760)	C₇H₁₆N₂	C, H, N
					...	270 dec (EtOH)	C₇H₁₆N₂·2HCl	C, H, N, Cl

[a] Picric acid.

TABLE III

R R'
\ /
C——CH₂
/ \
R''—N   NCH(C₆H₅)₂
\ /
CH—CH₂
|
CH₃

Compd	R	R'	R''	Yield, %	Bp (mm) or mp, °C	Formula	Analyses
VIIa	H	CH₃	H	45	150-155 (0.5) 79-80 (dil EtOH)	C₁₉H₂₄N₂	C, H, N
					290-295 (EtOH)	C₁₉H₂₄N₂·HCl	C, H, N, Cl
VIIb	H	CH(CH₃)₂	H	58	145-150 (0.6) 72-75 (Me₂CO)	C₂₁H₂₈N₂	C, H, N
					212-215 (EtOH-Et₂O)	C₂₁H₂₈N₂·HCl	
VIIc	CH₃	CH₃	H	58	94-96 (Me₂CO + H₂O)	C₂₀H₂₆N₂	C, H, N
VIIIa	H	CH₃	C₆H₅CH=CHCH₂	68	170-173 (EtOH)	C₂₈H₃₂N₂	C, H, N
VIIIb	H	CH(CH₃)₂	C₆H₅CH=CHCH₂	32	90-91 (Me₂CO + H₂O)	C₃₀H₃₆N₂	C, H, N
VIIIc	CH₃	CH₃	C₆H₅CH=CHCH₂	40	110 (EtOH)	C₂₉H₃₄N₂	C, H, N

in detail[3] and is based on the heating of the appropriate IV at 210-250° for 3-4 hr under atmospheric pressure. The crude V was isolated by distillation and purified by precipitating in ether the corresponding hydrochloride from which the free base was liberated with Na₂CO₃. Compound IVb failed to cyclize to V after heating for 4 hr at 250-260°.

2,6-Substituted 4-Benzylpiperazines (VIa-c, Table II). General Method.—A solution of 50 g of V in 500 ml of anhydrous ether was added under stirring to a suspension of 50 g of LiAlH₄ in 500 ml of ether, and the mixture was refluxed for 6 hr and worked up as described[3] for VIa.

2,6-Substituted Piperazines (Ia-c, Table II). General Method.—A solution of 0.1 mole of VI in 100 ml of EtOH was hydrogenated at atmospheric pressure over 10 g of 10% Pd-C. The catalyst was filtered and I was isolated by distillation of the filtrate.

2,6-Substituted 4-Benzhydrylpiperazines (VIIa-c, Table III). General Method.—A solution of 0.1 mole of Ia-c, 0.11 mole of benzhydryl chloride, 0.11 mole of Et₃N, and 100 ml of PhMe was refluxed for 35-40 hr. The reaction mixture was cooled and treated with 50 ml of 5% HCl. The aqueous layer was separated, made alkaline (Na₂CO₃), and extracted with ether. The extract was dried (Na₂SO₄) and the solvent was evaporated to give crude VII purified by distillation.

2,6-Substituted 1-Cinnamyl-4-benzhydrylpiperazines (VIIIa-c, Table III). General Method.—A solution of 0.05 mole of VII, 0.06 mole of cinnamyl chloride, 0.06 mole of Et₃N, and 200 ml of PhMe was refluxed for 48 hr. Into the reaction mixture, dry

HCl was bubbled on cooling, the solvent was decanted off, and the gummy precipitate was washed (Et₂O) and triturated with 100 ml of H₂O. The insoluble hydrochloride of VIII which solidified after standing was separated from the aqueous solution; the base VIII was liberated with 10% NaOH and was extracted (C₆H₆). The filtrate of the hydrochloride was made alkaline (NaOH) and extracted (Et₂O). From the dried and evaporated extract a variable amount of starting VII was recovered by distillation.

1-Propionyl-4-benzyl-2,6-dimethylpiperazine (IXa).—A mixture of 10 g of VIa and 15 g of propionic anhydride was heated at 100° for 1.5 hr, cooled, and poured into 40 ml of 10% HCl. The excess of propionic anhydride was extracted (Et₂O), and the acid solution was made alkaline with 10% NaOH and extracted (Et₂O). The extract was dried, the solvent was evaporated, and the residue was distilled to give 12.1 g (95%) of IXa, bp 140° (0.4 mm). *Anal.* (C₁₆H₂₄N₂O) C, H, N.

1-Propionyl-2,6-dimethylpiperazine (Xa).—A solution of 12 g of IXa in 100 ml of EtOH was hydrogenated at 50° and under 50 atm of initial hydrogen pressure in the presence of 3 g of 10% Pd-C. After 5 hr the catalyst was filtered off and the filtrate was distilled; yield 6.5 g (83%) of Xa, bp 93-95° (0.5 mm), n²⁰D 1.5057. *Anal.* (C₉H₁₈N₂O) C, H, N.

The **hydrochloride** melted at 155-157° (i-PrOH-Et₂O). *Anal.* (C₉H₁₉ClN₂O) Cl, N.

1-Propionyl-4-benzhydryl-2,6-dimethylpiperazine (XIa). A. From Xa.—A solution of 3.4 g (0.02 mole) of Xa, 4.45 g (0.022 mole) of benzhydryl chloride, 2.2 g (0.022 mole) of Et₃N, and

50 ml of PhMe was refluxed for 30 hr, $Et_3N \cdot HCl$ that precipitated was filtered off, the filtrate was evaporated, and the oily residue was treated with petroleum ether. A solid was separated and crystallized from EtOH; yield 3 g (44.5%) of XIa, mp 135–137°. *Anal.* ($C_{22}H_{28}N_2O$) C, H, N.

B. From VIIa.—A mixture of 0.5 g of VIIa and 2 g of propionic anhydride was heated at 100° for 1.5 hr then was cooled and poured into 10 ml of Na_2CO_3 solution. After stirring 15 min at room temperature to decompose the excess propionic anhydride, the mixture was extracted with ether, and the extract was dried to give 0.4 g of a solid which after crystallization from EtOH melted at 135–137° and was identical (mixture melting point and ir spectra) with XIa obtained from Xa.

Attempts to Synthesize 2,6-Substituted 1-Benzhydrylpiperazines.—A solution of 0.01 mole of VIa-c, 0.015 mole of benzhydryl chloride, 0.015 mole of Et_3N, and 50 ml of PhMe was refluxed for 48 hr. The clear solution was cooled and shaken with 20 ml of 10% HCl. The organic layer was evaporated and the residue was identified by ir analysis as crude benzhydryl chloride. The aqueous acid was made alkaline (Na_2CO_3) and was extracted (Et_2O). From the extract 90% of the starting VI was recovered by distillation.

Acknowledgment.—The authors are indebted to Dr. G. Pelizza and Mrs. A. Restelli for organic and microanalysis and to Dr. W. Zanichelli and to Dr. G. Schott for assistance in the compilation of the manuscript.

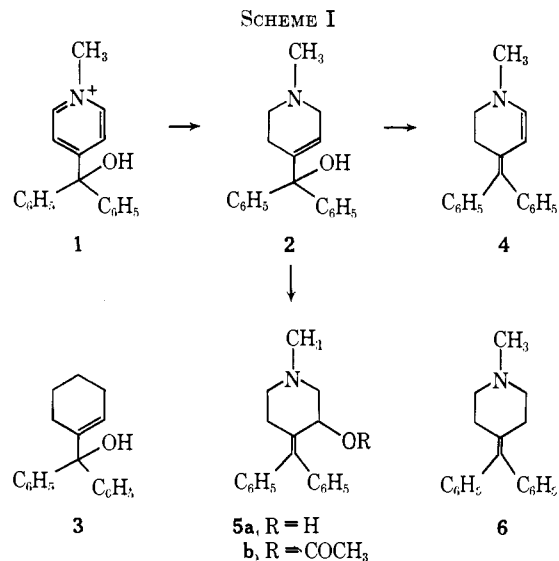# 3-Hydroxy-1-methyl-4-(diphenylmethylene)piperidine

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In 1956, Lyle and co-workers[2] reported an attempt to effect oxotropic allylic rearrangement of 1-methyl-α,α-diphenyl-1,2,3,6-tetrahydro-4-pyridinemethanol (2) analogous to that reported earlier for diphenylcyclohexen-1-ylmethanol (3) by Braude.[3] Using 2 N HCl in aqueous acetone, Lyle obtained only the enamine 4 and not the desired 3-hydroxy-1-methyl-4-(diphenylmethylene)piperidine (5a). Since the tertiary carbinol 2, earlier prepared from methyl 1-methyl-1,2,3,6-tetrahydroisonicotinate,[4] was readily available to us by sodium borohydride reduction of the quaternary salt of diphenyl-4-pyridinemethanol (1), a reinvestigation of the oxotropic allylic rearrangement was undertaken (see Scheme I).

After some experimentation we found that treatment of 2 with 1 N aqueous HCl at room temperature for 24 hr resulted in quantitative conversion to 3-hydroxy-1-methyl-4-(diphenylmethylene)piperidine (5a), obtained as the free base, mp 109–110°, or hydrochloride salt, mp 230°. It was converted to the acetate 5b, mp 171–172°, as the acid maleate salt. The structure of 5a was confirmed by its nmr spectrum that showed an α-hydroxycarbinyl proton at τ 5.56 ppm and a hydroxyl

(1) To whom inquiries should be addressed.

(2) G. G. Lyle, E. F. Perlowski, and R. E. Lyle, *J. Org. Chem.*, **21**, 423 (1956).

(3) E. A. Braude and J. A. Cross, *J. Chem. Soc.*, 2014 (1950); see also E. A. Braude, *Quart. Rev.* (London), **4**, 404 (1950).

(4) (a) R. E. Lyle, E. F. Perlowski, H. J. Troscianiec, and G. G. Lyle, *J. Org. Chem.*, **20**, 1761 (1955); (b) R. E. Lyle and G. G. Lyle, *J. Am. Chem. Soc.*, **76**, 3536 (1954).

SCHEME I

proton at τ 5.88 ppm that disappeared on addition of deuterium oxide in the presence of sodium deuterate.

Our interest in the rearrangement product 5 arose from its structural relationship to 1-methyl-4-(diphenylmethylene) piperidine (6) that, as the quaternary salt, is in clinical use as an anticholinergic agent (diphemamil),[5] and the fact that 5 contains an ethanolamine moiety in common with the biogenetic catecholamines and some of their antagonists.[6] Comparison of *in vitro* anticholinergic activity (guinea pig ileum) of 5a and 6 (as tertiary amine salts) showed 5a to be less active by a factor of 100. Compounds 5a and b increased spontaneous motor activity in mice and rats. Screening for anorexic activity (eating behavior of mice[7] and food consumption in rats)[8] showed little or no such activity. Compound 5b both prevented (ED_{50} = 15 mg/kg *po*) *and* remitted ptosis induced by 2 mg/kg iv of reserpine in mice at 15–30 mg/kg *po*.[9] These data suggest that 5a and 5b possess weak sympathomimetic properties.[10] Compounds 5a and 5b inhibited mustard-induced hind foot edema[11] in rats at 30 and 10 mg/kg/day *po* given about 18 hr before and just before the mustard, respectively. Essentially no inhibition of edema was observed at these doses in adrenalectomized rats. Compound 5a was also evaluated for its effect on the relative weight (mg/100 g of body weight) of the endocrine organs of the intact immature rat. At 50 mg/kg/day sc for 10 days, it reduced the rate of body weight gain to 61% of control and body growth to 76% of control. The endocrine and endocrine-influenced organs which varied by more than 20% from the control were ventral prostate, 79%; epididymal fat body, 78%; thymus, 64%; and spleen, 69%.

These evaluations failed to suggest therapeutic utility for 5a and 5b.

(5) N. Sperber, F. J. Villani, M. Sherlock, and D. Papa, *ibid.*, **73**, 5010 (1951).

(6) R. A. McLean in "Medicinal Chemistry," A. Burger, Ed., 2nd ed, Interscience Publishers, Inc., New York, N. Y., 1960, p 592.

(7) By a procedure described by H. J. Keffeler, D. L. Braun, and A. Kandel, *Pharmacologist*, **9**, 244 (1967); D. L. Braun, H. J. Keffeler, C. L. Wright, and A. Kandel, *ibid.*, **9**, 244 (1967).

(8) By an unpublished modification of a method by J. Spengler and P. Waser, *Arch. Exp. Pathol. Pharmakol.*, **237**, 171 (1959).

(9) *Cf.* A. Kandel, *Fed. Proc.*, **25**, 385 (1966).

(10) We thank Drs. T. H. Tsai and A. Kandel for these test result data.

(11) A. C. Levy, T. H. Beaver, R. D. Strain, and D. E. Holtkamp, *Proc. Soc. Exp. Biol. Med.*, **111**, 576 (1962).