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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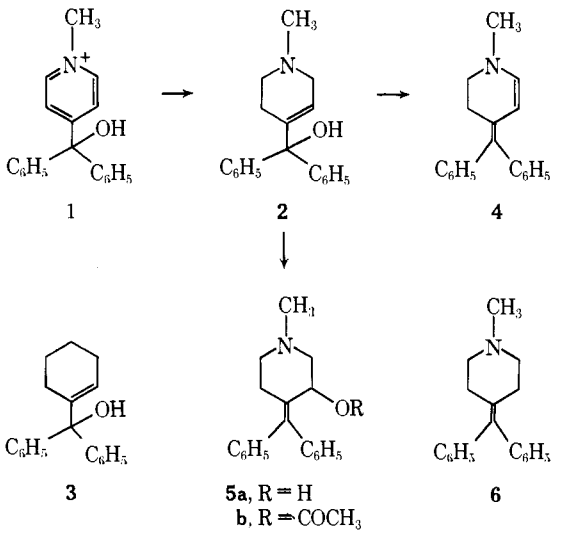
In 1956, Lyle and co-workers[2] reported an attempt to effect oxotropic allylic rearrangement of 1-methyl-α,α-diphenyl-1,2,3,6-tetrahydro-4-pyridinemethanol (**2**) analogous to that reported earlier for diphenylcyclohexen-1-ylmethanol (**3**) by Braude.[3] Using 2 *N* HCl in aqueous acetone, Lyle obtained 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).

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 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**.

(1) To whom inquiries should be addressed.

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(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).

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

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Experimental Section[12]

1-Methyl-α,α-diphenyl-1,2,3,6-tetrahydro-4-pyridinemethanol (2).—A mixture of 100 g (0.38 mole) of diphenyl-4-pyridinemethanol, 100 ml of dioxane, and 50.5 g (0.40 mole) of Me_2SO_4 was heated on a steam bath for about 30 min, the solvent was removed under vacuum, and the resulting residue was dissolved in *i*-PrOH. The pyridinium salt **1** was precipitated by addition of 1.5 vol of petroleum ether (bp 75–90°); 136 g, mp 169–171°. It was dissolved in a mixture of 1 l. of H_2O, 2 l. of MeOH, and 50 ml of 50% aqueous NaOH. The reaction flask was cooled in an ice bath and a solution of 77 g of $NaBH_4$ in 400 ml of H_2O was added dropwise. Cooling was continued for 2 hr after which time the mixture was heated on a steam bath to allow evaporation of methanol. The product crystallized from the reaction mixture on cooling, was collected, washed (H_2O), and recrystallized from EtOAc to give 95.5 g (85% yield) of **2**: mp 179–180.5° (lit.[4b] mp 179.0–179.8°); λ_{max} (MeOH) 248 mμ (ε 282), 253 (368), 259 (446), 265 (343).

Anal. Calcd for $C_{19}H_{21}NO$: C, 81.68; H, 7.58; N, 5.01. Found: C, 81.67; H, 7.55; N, 4.89.

3-Hydroxy-1-methyl-4-(diphenylmethylene)piperidine (5a) and Acetate (5b).—A mixture of 25.0 g of carbinol **2** and 500 ml of 1 *N* HCl was stirred for 24 hr. The resulting clear red solution was neutralized with concentrated NH_4OH and the product was extracted into ether. The extract was washed (H_2O) and dried (Na_2SO_4) and the product, obtained after evaporation of solvent, was recrystallized once from ether to give 23.5 g (94% yield) of **5a**: mp 109–110°; λ_{max} (MeOH) 225.5 mμ (ε 13,600), broad shoulder at higher wavelength.

Anal. Calcd for $C_{19}H_{21}NO$: C, 81.68; H, 7.58; N, 5.01. Found: C, 81.84; H, 7.61; N, 4.97.

A hydrochloride salt was prepared, mp 230°, that also analyzed correctly for C, H, and N. The acetate **5b** was prepared by heating **5a** in excess Ac_2O–pyridine (10:1) for 1 hr on a steam bath. The product, obtained after conventional work-up, was converted to the acid maleate salt and recrystallized from *i*-PrOH, mp 171–172°.

Anal. Calcd for $C_{21}H_{23}NO_2 \cdot C_4H_4O_4$: C, 68.63; H, 6.22; N, 3.20. Found: C, 68.74; H, 6.24; N, 3.19.

(12) We are indebted to Dr. H. J. Keily, M. J. Gordon, and associates for microanalyses and spectral data.

Dihydropyrrolo[3,4-*c*]pyrazoles

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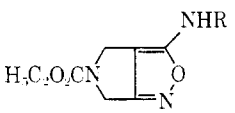
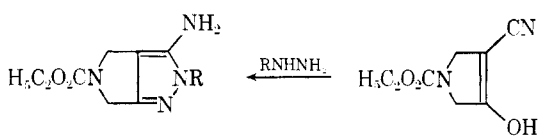
In view of the hypotensive activity observed for a number of dihydropyrrolo[3,4-*c*]isoxazoles (I) in experimental animals,[1] we undertook the syntheses of the isosteric dihydropyrrolo[3,4-*c*]pyrazoles (II).



I



II III

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The 3-aminopyrrolopyrazole derivatives, listed in Table I, were prepared by condensing a cyano ketone (III) with a salt of the appropriate hydrazine.[2] The 5-acetyl compound **17** was obtained by a similar condensation of 1-acetyl-4-cyano-3-oxopyrrolidine[3] with phenylhydrazine hydrochloride. In view of the increased hypotensive activity seen in the isoxazole series for the N-acetyl derivative, several acylated derivatives of II (Table II) were prepared. Compound **3** when acetylated with either acetic anhydride alone or acetyl chloride and pyridine gave the acetyl derivative **19**. If pyridine was used along with the anhydride the product was a diacetyl derivative **27**. Compounds **20** and **23** were obtained by the usual benzoylation procedure.

Unlike the 3-aminopyrrolo[3,4-*c*]isoxazoles,[1] none of the compounds listed in the two tables showed significant hypotensive activity.

Experimental Section[4]

Methyl N-(2-Cyanoethyl)-2-methylalaninate (IV).—The base prepared from 40 g (0.26 mole) of methyl 2-methylalaninate hydrochloride by the addition of 16 g (0.29 mole) of KOH in 25 ml of H_2O was treated gradually at 0° with 19.4 g (0.36 mole) of acrylonitrile. The mixture was then heated at 70–80° for 1 hr. An oil formed, which was extracted with Et_2O, and the Et_2O layer was distilled. The nitrile ester weighed 26 g (42%), bp 95–96° (1 mm), $n^{22}D$ 1.4470. *Anal.* ($C_8H_{15}N_2O_2$) C, H, N.

Methyl N-Carbethoxy-N-(2-cyanoethyl)-2-methylalaninate (V).—An ice-cold mixture containing 8.22 g (0.045 mole) of the preceding cyano ester, 3.8 g (0.045 mole) of $NaHCO_3$, and 15 ml of H_2O was treated with 4.5 g (0.045 mole) of ethyl chlorocarbonate. The mixture was stirred for 2 hr and the acylated ester was extracted and distilled. The ester weighed 7.8 g (73%), bp 128–130° (0.5 mm). *Anal.* ($C_{11}H_{18}N_2O_4$) C, H; N: calcd, 11.6; found, 12.1.

N-Carbethoxy-2,2-dimethyl-4-cyano-3-pyrrolidone (VI).—A mixture of 9.9 g (0.045 mole) of the above cyano ester, 2.2 g (0.045 mole) of NaOMe, and C_6H_6 (50 ml) was refluxed for 3 hr. The resultant sodium salt was filtered off and dissolved in H_2O and the pyrrolidone was liberated by acidifying with 50 ml of 1 *N* HCl. The crystalline product, 6.5 g (82%), was recrystallized from EtOH; mp 127–129°. *Anal.* ($C_{10}H_{14}N_2O_3$) C, H, N.

Ethyl 3-Amino-2-ethyl-2,6-dihydropyrrolo[3,4-*c*]pyrazole-5-(4H)-carboxylate (2).—A solution containing 2.0 g (0.01 mole) of 1-carbethoxy-4-cyano-3-pyrrolidone monohydrate,[1] 1.33 g (0.01 mole) of ethyl hydrazine dihydrochloride, and 20 ml of EtOH was refluxed for 3 hr. The gum, which was obtained on evaporation of the mixture, was dissolved in a minimum amount of H_2O and rendered basic with 10 *N* NaOH, and the crude pyrazole which precipitated was collected and dried *in vacuo*.

Ethyl 3-Amino-2-phenyl-2,6-dihydropyrrolo[3,4-*c*]pyrazole-5-(4H)-carboxylate (3).—A mixture containing 8.0 g (0.04 mole) of 1-carbethoxy-4-cyano-3-pyrrolidone monohydrate,[1] 5.8 g (0.04 mole) of phenyl hydrazine hydrochloride, and 100 ml of EtOH was refluxed for 5 hr. The solvent was removed under diminished pressure and the residual gum was dissolved in 100 ml of 5 *N* HCl and decolorized with charcoal. Basifying the filtrate with 60 ml of 10 *N* NaOH, with caution, gave a solid which was recrystallized from 95% EtOH.

The other compounds listed in Table I were prepared similarly.

Ethyl 3-Acetamido-2-phenyl-2,6-dihydropyrrolo[3,4-*c*]pyrazole-5(4H)-carboxylate (21).—A mixture prepared by a gradual addition of 2.72 g (0.01 mole) of ethyl 3-amino-2-phenyl-2,6-dihydropyrrolo[3,4-*c*]pyrazole-5(4H)-carboxylate (**3**) to 40 ml of Ac_2O was heated on a steam bath for 0.5 hr. The solution on evaporation gave a solid which was recrystallized twice from C_6H_6.

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