Admixture of this compound with authentic glyoxal osazone did not depress the melting point.

2-Ethoxy-1,4-dioxane.—A solution of 5 g. of IIIa in 100 ml. of absolute ethanol, to which 0.1 g. of anhydrous potassium carbonate and 0.4 g. of 10% palladium-on-charcoal had been added, was treated with hydrogen at 30 pounds pressure and room temperature. Reduction was complete in three minutes, and the catalyst was removed from the resulting mixture by filtration. The filtrate was concentrated and the concentrate was fractionated at reduced pressure. A total of 3.5 g. of 2-ethoxy-1,4-dioxane was obtained, b.p. 53–53.5° (11 mm.), $n^{25}D$ 1.4248. Published constants[7] for this compound are: b.p. 61° (17 mm.), $n^{20}D$ 1.4260.

Anal. Calcd. for $C_6H_{12}O_3$: C, 54.53; H, 9.15. Found: C, 54.73; H, 9.44.

The 2,4-dinitrophenylhydrazone of (2-hydroxyethoxy)-acetaldehyde (the aldehyde derived from this cyclic acetal) was prepared from this product according to the published method,[4,7] and yellow crystals melting at 136.5–139° were obtained. Admixture with the authentic 2,4-dinitrophenylhydrazone did not depress the melting point.

5-Methoxy-1,4-dioxene-2 (IIIb).—The preparation of this compound was accomplished by a procedure similar to that described above for the ethoxy analog. From 21.5 g. (0.145 mole) of a mixture of *cis*- and *trans*-IIb there was obtained 11.5 g. (68.5% yield) of IIIb, b.p. 39–40° (11 mm.), $n^{25}D$ 1.4359.

Anal. Calcd. for $C_5H_8O_3$: C, 51.72; H, 6.94. Found: C, 51.67; H, 7.15.

2-Methoxy-1,4-dioxane.—The reduction of IIIb was carried out in the same manner as that of the ethoxy analog, and 2-methoxy-1,4-dioxane was obtained, b.p. 38–39° (11 mm.), $n^{25}D$ 1.4238.

Anal. Calcd. for $C_5H_{10}O_3$: C, 50.83; H, 8.53. Found: C, 51.14; H, 8.79.

The 2,4-dinitrophenylhydrazone of (2-hydroxyethoxy)-acetaldehyde was prepared from this compound and melted at 137–139°. Admixture with authentic material did not depress the melting point.

Attempts to Obtain *p*-Dioxadiene (V).—Vapor-phase dealkoxylation experiments with both dialkoxydioxanes were carried out in which the temperature was varied between 200 and 375°, and the nitrogen flow rate was varied between 0.25 and 0.6 l./min. In none of these experiments could *p*-dioxadiene[11] be separated by careful fractionation of the alcohol portion of the effluent. Attempts to isolate the stable 2,3,5,6-tetrachloro-1,4-dioxane derivative of *p*-dioxadiene[11] by chlorination of the fractions with chlorine in carbon tetrachloride were unsuccessful. Finally, the ultraviolet spectrum of several fractions, at a dilution of 1:4000, showed extremely little absorption and no peak at 250 mμ.[8]

In some of these vapor-phase experiments extensive decomposition occurred, as evidenced by the deposition of carbon on the alumina and by the formation of appreciable quantities of water and non-condensable gases.

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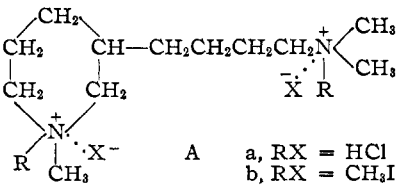
Synthetic Hypotensive Agents. III. Some 4,4′-Bipiperidines

BY ARTHUR P. PHILLIPS AND JOHN MENTHA

RECEIVED MAY 23, 1955

In an earlier study[1] strong ganglionic blocking action was discovered among some hydrogenation products of nicotine derivatives. Both the bis tertiary amine A_a and its bis-methiodide A_b were potent ganglionic blocking agents. The structural resemblance between A_b and hexamethonium salts was immediately apparent. Since the incorporation of a portion of the hexamethonium chain into a piperidine ring (A_a and A_b) had resulted in ganglionic blockers of high potency, it seemed desirable to investigate the pharmacological properties of some similar compounds in which the entire six carbon chain of hexamethonium is held in not one but two joined piperidine rings. This paper reports the preparation of a series of such compounds, some 4,4′-bipiperidines and various of their derivatives.



A a, RX = HCl
b, RX = CH_3I

The 4,4′-bipiperidines were obtained by catalytic hydrogenation of suitable 4,4′-bipyridines. 4,4′-Bipyridine (I) itself was the central starting compound and was readily prepared by the method of Dimroth and co-workers.[2,3] These workers reduced pyridine, with zinc dust in acetic anhydride solution, to 1,1′-diacetyl-1,1′,4,4′-tetrahydro-4,4′-bipyridine which was then air oxidized to 4,4′-bipyridine (I) either in alcohol or acetic acid solution.

Figure 1 outlines the various reaction sequences employed to go from 4,4′-bipyridine (I) to the desired products. Catalytic hydrogenation of I dihydrochloride in aqueous methanol using Adams catalyst gave 4,4′-bipiperidine (II) which has been described previously by several groups of workers.[4-6] This disecondary amine II was methylated by two different methods. When II was alkylated with excess methyl iodide in methanol solution in the presence of sodium hydroxide the diquaternary salt N,N′-dimethyl-4,4′-bipiperidine dimethiodide IVa was obtained directly. Alternatively, II was methylated with formaldehyde and formic acid by the method of Eschweiler[7] and Clarke,[8] and in this way the ditertiary amine, N,N′-dimethyl-4,4′-bipiperidine (III), was obtained in excellent yield. The ditertiary amine III was subsequently quaternized with various alkyl halides, such as methyl, ethyl and propyl iodides to give the diquaternary salts IV (a, b and c).

These same diquaternary salts IV (a, b and c) of Fig. 1, were prepared by an alternate route which made accessible a variety of ditertiary amines of structure VI, Fig. 1, as intermediates. In this method 4,4′-bipyridine (I), was diquaternized by reaction with the desired organic halide to give the diquaternary salts V and these, upon catalytic hydrogenation over Adams catalyst, gave the ditertiary amines VI. Quaternization of the ditertiary amines VI with methyl iodide gave the same series of diquaternary salts IV obtained by the other route.

The 1,1′,4,4′-tetrahydrobipyridine structure is

(1) A. P. Phillips, THIS JOURNAL, **76**, 2211 (1954).

(2) O. Dimroth and R. Heene, *Ber.*, **54**, 2934 (1921).
(3) O. Dimroth and F. Frister, *ibid.*, **55**, 3693 (1922).
(4) C. R. Smith, THIS JOURNAL, **50**, 1936 (1928).
(5) H. King and T. S. Work, *J. Chem. Soc.*, 1307 (1940).
(6) E. P. Hart, *ibid.*, 3872 (1953).
(7) W. Eschweiler, *Ber.*, **38**, 880 (1905).
(8) H. T. Clarke, H. B. Gillespie and S. Z. Weisshaus, THIS JOURNAL, **55**, 4571 (1933).

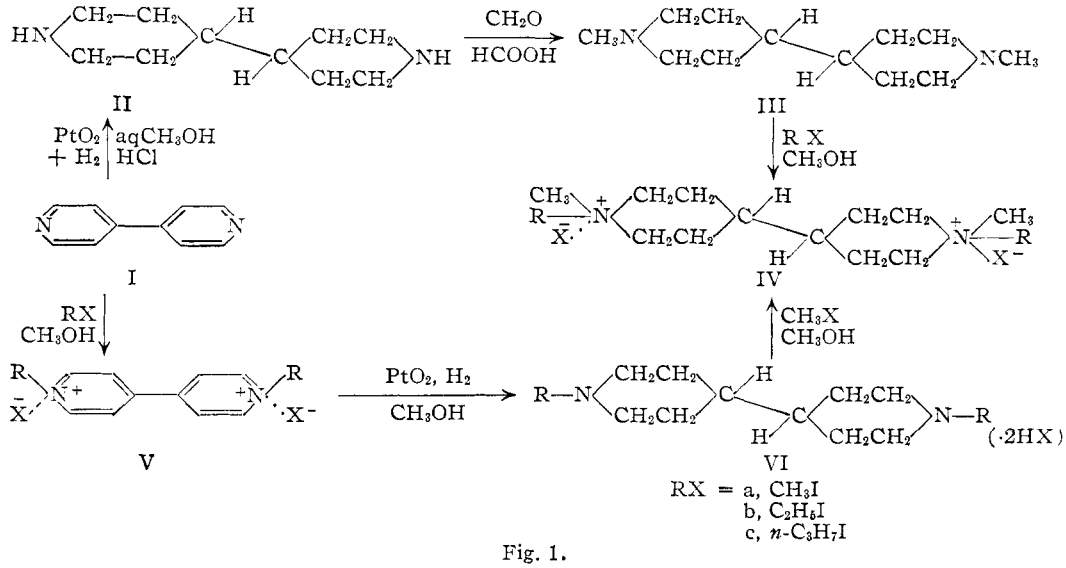


Fig. 1.

somewhat labile and certain compounds of this type are readily transformed into related pyridine derivatives. In the catalytic hydrogenation of the various bipyridines, if such tetrahydrobipyridines should be intermediates, it seemed to be at least possible that some of the bipyridine structure might be ruptured to give simple piperidines as the products. Since the ordinary analytical methods employed would not distinguish the simple piperidine compounds from the corresponding bipiperidines, and since melting points and solubilities of certain of the simple piperidine salts were not found in the literature, several of the lower alkyl quaternary iodides were made from N-methylpiperidine for purposes of comparison. These differed significantly in physical properties from the corresponding bipiperidines prepared by the methods shown in Fig. 1.

Surprisingly, none of the bipiperidine derivatives made (secondary, tertiary or quaternary) were ganglionic blocking agents. Only the disecondary amine 4,4'-bipiperidine lowered blood pressure to a significant extent in experimental animals, but this hypotensive effect was due to histamine liberation and not to ganglionic block.

Experimental

4,4'-Bipyridine, m.p. 112–113°, was prepared by the method of Dimroth and co-workers.[2,3]

4,4'-Bipyridine Dimethiodide.[9]—A solution of 4,4'-bipyridine and excess methyl iodide (4 moles) in methanol was refluxed for 20 hours. In about 30 minutes insoluble orange-red crystals started to precipitate. After cooling, the crystals were filtered off and were purified by several recrystallizations from water–acetone mixtures. This compound was nearly insoluble in methanol, ethanol or acetone, but was easily soluble in water in which it gave a nearly colorless solution, and the orange-red crystals were reprecipitated upon the addition of acetone. The yield was greater than 90%; m.p. > 330°.

Anal. Calcd. for $C_{12}H_{14}N_2I_2$: C, 32.7; H, 3.2. Found: C, 33.0; H, 3.2.

From the methanol mother liquors of the 4,4'-bipyridine dimethiodide there was obtained another compound which was deep purple-red in color. This was isolated in a yield of about 2%, and was almost insoluble in water, but moderately soluble in hot methanol. It was purified by recrystallization from methanol, melted then at 221–222°, and gave analyses corresponding to 4,4'-bipyridine dimethiodide diperiodide.

Anal. Calcd. for: $C_{12}H_{14}N_2I_6$: C, 15.2; H, 1.5. Found: C, 15.5; H, 1.8.

4,4'-Bipyridine Diethiodide.[10]—A solution of 4,4'-bipyridine in methanol containing an excess (4 moles) of ethyl iodide was refluxed for 20 to 30 hours and gave orange-red crystals of the diethiodide, yield 80–90%, m.p. 273–274° after recrystallizations from aqueous acetone and from methanol.

Anal. Calcd. for $C_{14}H_{18}N_2I_2$: C, 35.9; H, 3.9. Found: C, 35.8; H, 3.9.

In this case, also, the mother liquors yielded about 2% of a dark purple-red solid, insoluble in water, but moderately soluble in much hot methanol. After recrystallization from methanol it melted at 208–209° and gave analyses corresponding with 4,4'-bipyridine diethiodide diperiodide.

Anal. Calcd. for $C_{14}H_{18}N_2I_6$: C, 17.2; H, 1.9. Found: C, 17.9; H, 2.2.

4,4'-Bipiperidine has been described earlier[4–6] and for this work was made by a procedure similar to that of Smith[4] by catalytic hydrogenation of 4,4'-bipyridine over Adams catalyst in aqueous methanol made strongly acid with hydrochloric acid. The hydrogenation at 4 atmospheres pressure and room temperature went slowly and took seven to eight hours to reduce 0.05 mole of compound. The yield of dihydrochloride, m.p. > 310°, was greater than 90%, and this on addition of alkali gave the base m.p. 167–168°.

N,N'-Dimethyl-4,4'-bipiperidine. A. Dihydroiodide.—A solution of 4.4 g. (0.01 mole) of 4,4'-bipyridine dimethiodide in 150 cc. of water was hydrogenated in a Burgess–Parr type machine using 0.2 g. of platinum oxide (Adams) catalyst and 3 to 4 atmospheres hydrogen pressure and at room temperature. Hydrogen uptake was rapid and was completed with the absorption of six moles of hydrogen per mole, within one hour. The platinum was removed by filtration and the aqueous filtrate was evaporated to dryness *in vacuo*. The residue was recrystallized several times from methanol and from methanol–ethyl acetate mixtures and gave 4.4 g. (100%) of nearly white crystals, m.p. 304–305°.

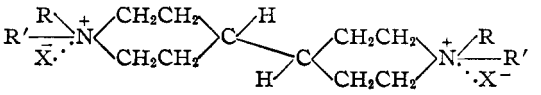
B. Dihydrochloride.—A mixture of 8.4 g. (0.05 mole) of 4,4'-bipiperidine, 10 cc. of 98% formic acid and 10 cc. of

(9) 4,4'-Bipyridine dimethiodide was made by H. Weidel and M. Russo, *Monatsh.*, **3**, 850 (1882), but they did not characterize it by melting point or analysis. More recently, B. Emmert and J. Starvitz, *Ber.*, **56**, 83 (1923), have made a series of 4,4'-bipyridine mono and dialkyl quaternary salts, their interest being in the unusual color behavior of these compounds. The latter authors, too, did not characterize the salts reported in this paper by melting point and gave only iodide analytical results.

(10) Prepared previously by Emmert and Starvitz (see reference 9) but no yield or melting point was reported, and only iodide analysis was given.

TABLE I

4,4′-BIPIPERIDINES



R	R′X	M.p., °C.[a]	Crystn. solvent[b]	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
H	HCl[c]	310	M	$C_{10}H_{22}N_2Cl_2$	49.8	49.9	9.2	9.0
CH_3	HCl[d]	320–322	A	$C_{12}H_{26}N_2Cl_2$	53.5	53.1	9.7	9.6
CH_3	HI[e]	304–305	M	$C_{12}H_{26}N_2I_2$	31.8	31.7	5.8	5.7
C_2H_5	HI[f]	312–314	M	$C_{14}H_{30}N_2I_2$	35.0	35.2	6.3	6.2
CH_3	CH_3I[g]	320	W.Ac	$C_{14}H_{30}N_2I_2$	35.0	34.9	6.3	6.1
CH_3	C_2H_5I[h]	293–295	A	$C_{16}H_{34}N_2I_2$	37.8	38.0	6.7	6.7
CH_3	n-C_3H_7I	218–219	M	$C_{18}H_{38}N_2I_2$	40.3	40.5	7.2	7.3

[a] Melting points are uncorrected; yields in general were greater than 90%. [b] A = ethanol; Ac = acetone; M = methanol; W = water. [c] The base, m.p. 167–168°, crystals from benzene, has been described earlier, see references 4, 5, 6. [d] From 4,4′-bipiperidine, formaldehyde and formic acid by the Eschweiler[7]–Clarke[8] method. [e] By catalytic hydrogenation of 4,4′-bipyridine dimethiodide. [f] By catalytic hydrogenation of 4,4′-bipyridine diethiodide. [g] Prepared in three ways as shown in Fig. 1. [h] Made by two routes as shown in Fig. 1.

37% aqueous formalin was heated on a steam-bath for three to four hours. Another 5 cc. of formic acid and 5 cc. of formalin was added and heating was continued for one more hour. Methanol, 100 cc., and concentrated hydrochloric acid, 15–20 cc., were added and the solution was evaporated to dryness. The residue was purified by recrystallization from methanol, and from ethanol, m.p. 320–322°.

After liberation of the free base, N,N′-dimethyl-4,4′-bipiperidine, with alkali several diquaternary salts were prepared from it by refluxing in methanol solution with the appropriate alkyl halide. Details for all the bipiperidines are summarized in Table I.

A few simple derivatives of N-methylpiperidine have been prepared for comparison of their melting points and solubilities with the almost isomeric bipiperidine derivatives. This was felt to be desirable because ordinary analytical results would not distinguish the two series of compounds. The melting points and solubilities of the mono- and bipiperidine derivatives were different in each case, and the monopiperidine compounds were much more easily soluble in alcohols than the bipiperidines.

N-Methylpiperidine[11] was made by the Eschweiler[7]–Clarke[8] methylation of piperidine and its hydrochloride melted at 211–212°, after recrystallization from ethanol–ether mixtures.

N-Methylpiperidine methiodide[12–14] melted above 340°, and was crystallized from methanol–ether mixtures.

N-Methylpiperidine ethiodide, m.p. 304–305°, from methanol–ether. *Anal.* Calcd. for $C_8H_{18}NI$: C, 37.7; H, 7.1. Found: C, 37.7; H, 6.9.

N-Methylpiperidine *n*-propiodide, m.p. 179–180°, from ethanol–ether. *Anal.* Calcd. for $C_9H_{20}NI$: C, 40.1; H, 7.5. Found: C, 40.4; H, 7.5.

Acknowledgment.—The authors are indebted to Mr. Samuel W. Blackman for the microanalyses included and to Dr. Kenneth Colville for the pharmacological results summarized here.

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Disproportionation of Phenylsilanes with Aluminum Chloride as the Catalyst

BY JOHN L. SPEIER AND RUTH E. ZIMMERMAN[1]

RECEIVED JULY 14, 1955

Disproportionation of groups attached to silicon in certain silanes has been observed numerous times. A very early account describing disproportionation is given by Friedel and Ladenburg[2a] who treated triethoxysilane with sodium to form silane according to the equation

$$4(EtO)_3SiH \longrightarrow 3(EtO)_4Si + SiH_4$$

More recently Benkeser[2b] and co-workers have described disproportionation reactions of silanes of the type $(C_6H_5)_xSiCl_{4-x}$, $(C_6H_5)_xSiH_{4-x}$ and $(C_6H_5)_xMe_ySiH_{4-x-y}$ in the presence of sodium or sodium–potassium alloy. Reactions very similar to these recently have been discovered in our laboratory to occur very smoothly and rapidly under the influence of aluminum chloride.

During the course of a series of experiments occasion arose to add a small amount of aluminum chloride to a dilute benzene solution of phenylsilane at room temperature. Immediately a gas was produced, the mixture began to bubble and a violent explosion shattered the flask. With suitable precautions the experiment was repeated in a flask under a stream of dry nitrogen. Again a gas was produced which ignited spontaneously and burned in air with a bright flame at the outlet of the system producing clouds of silica soot.

Investigation into the cause of this unexpected behavior showed that phenylsilane disproportionated quantitatively in the presence of aluminum chloride according to the equation

$$4C_6H_5SiH_3 \longrightarrow (C_6H_5)_4Si + 3SiH_4 \qquad \text{I}$$

Further, this type of change also occurred with phenylmethylsilane and phenylchlorosilane.

$$4C_6H_5MeSiH_2 \longrightarrow (C_6H_5)_4Si + 2MeSiH_3 + Me_2SiH_2 \qquad \text{II}$$

$$5C_6H_5ClSiH_2 \longrightarrow (C_6H_5)_2SiCl_2 + (C_6H_5)_3SiCl + SiH_4 + 2SiH_3Cl \qquad \text{III}$$

The speed of the reaction in benzene solution at room temperature or slightly above and the quantitative description of the changes described by equations I and II are surprising, especially in the case II where a methyl group is involved.

Experimental

Phenylsilane (27 g., 0.25 mole) in 19.5 g. of benzene in a flask equipped with a condenser and a tube through which dry nitrogen was blown over the liquid was treated with one lump (0.5 g.) of aluminum chloride at 29°. Bubbles of

(1) Corning Glass Works and Dow Corning Corporation multiple fellowship.

(2) (a) C. Friedel and A. Ladenburg, *Ann.*, **143**, 124 (1867); (b) R. A. Benkeser, H. Landesman and D. J. Foster, *ibid.*, **74**, 648 (1952); R. A. Benkeser and D. J. Foster, *ibid.*, **74**, 4200 (1952); **74**, 5314 (1952).