Apparatus and Procedure.—The apparatus and procedure used were the same as those described previously.[4] The product from the reaction was distilled and the various fractions were analyzed by means of infrared spectroscopy.

Nickel-Kieselguhr.—This catalyst was obtained from Harshaw Chemical Co. in $^1/_8$ inch cylindrical pills. It contained 44% of nickel. Prior to use, it was reduced in a stream of hydrogen at 350°.

3,3-Dimethyl-1-butene was obtained by the pyrolysis of pinacolyl acetate. The latter was passed over glass wool in a nitrogen atmosphere at 400°.[5] It distilled at 41.2–41.7°, n^{20}D 1.3758.

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(4) V. N. Ipatieff, F. J. Pavlik and H. Pines, THIS JOURNAL, **75**, 3179 (1953).

(5) J. P. Wibaut and A. J. van Pelt, Jr., *Rec. trav. chim.*, **57**, 1055 (1938); **60**, 55 (1941).

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The Product Derived from the Cyclization of Triglycine Azide

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RECEIVED SEPTEMBER 6, 1955

In describing a new method for the synthesis of macrocyclic peptides we reported[1] the preparation from triglycine azide of a compound to which was assigned tentatively the structure cyclo-(triglycyl). Molecular weight determinations, which were incomplete at the time of the previous publication, have now shown the compound to be the dimer, cyclo-(hexaglycyl). The methods of freezing point depression and boiling point elevation failed to give reproducible molecular weight values, presumably due to the very low solubility of the compound under the conditions employed. An X-ray unit cell measurement[2] did not distinguish between the cyclo-(triglycyl) and cyclo-(hexaglycyl) possibilities.

However, by the method of isothermal distillation[3] using water as the solvent and dextrose as the standard, a molecular weight of 344 was obtained [calcd. for cyclo-(hexaglycyl) 342.31]. Very recently cyclo-(hexaglycyl) was reported[4] as a reaction product of the polymerization of N-carboxyglycine anhydride. At our request, Dr. C. H. Bamford kindly furnished a sample of his product for comparison. The infrared spectra (potassium bromide pellet) of the samples were superimposable over the range 2–15 μ. A mixed solubility study provided further evidence of identity. Dr. Bamford (private communication) informs us that his group has independently conducted a careful study of the nature of the products obtained by the two methods.

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(1) J. C. Sheehan and W. L. Richardson, THIS JOURNAL **76**, 6329 (1954).

(2) The authors are indebted to Prof. D. P. Shoemaker of this Department for the X-ray analysis.

(3) N. D. Cheronis, "Micro and Semimicro Methods of Techniques of Organic Chemistry," Vol. VI, edited by A. Weissberger, Interscience Publishers, Inc., New York, N. Y., 1954, pp. 228–229.

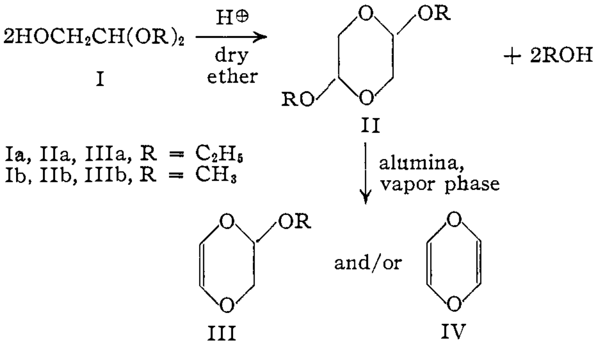
(4) D. G. H. Ballard, C. H. Bamford and F. J. Weymouth, *Proc. Royal Soc. (London)*, **227A**, 155 (1955).

Heterocyclic Vinyl Ethers. X. Dialkoxy 1,4-Dioxanes and Alkoxy 1,4-Dioxenes[1]

BY WILLIAM E. PARHAM AND HARRY E. REIFF

RECEIVED JULY 21, 1955

In paper III[2] of this series, a preparation of 1,4-dithiadiene was reported which involved the dealkoxylation of 2,5-diethoxy-1,4-dithiane, which was in turn prepared by the acid-catalyzed condensation of two molecules of mercaptoacetaldehyde diethyl acetal. An investigation of the analogous reactions in the oxygen series appeared to be of interest, and the following reaction sequence has been examined.



Hydroxyacetaldehyde diethyl acetal (Ia) has been prepared previously by reaction of ethanolic potassium hydroxide with bromoacetal at elevated temperatures.[3] However, variations in the published values for the refractive index and density of the product of this reaction[3b] indicated that varying amounts of ethoxyacetaldehyde diethyl acetal were present. Furthermore, we have observed that treatment of chloroacetal with alcoholic potassium hydroxide at elevated temperatures affords a 70% yield of ethoxyacetaldehyde diethyl acetal. Since hydroxyacetaldehyde dialkyl acetals, free of other acetals, were required for the preparation of the dialkoxydioxanes IIa and b, the following reactions leading to these acetals were investigated. Reaction of sodium benzyloxide (V) and bromoacetal (VIa) or dimethylchloroacetal (VIb) afforded the corresponding benzyloxyacetaldehyde dialkyl acetals (VII) in yields of 75–82%. The benzyloxyacetals were cleaved smoothly with sodium in liquid ammonia to give pure hydroxyacetals in good yield.

$$\underset{\text{V}}{C_6H_5CH_2ONa} + \underset{\text{VI}}{X\ CH_2CH(OR)_2} \longrightarrow$$

$$\underset{\text{VII}}{C_6H_5CH_2OCH_2CH(OR)_2} \xrightarrow[\text{liq. NH}_3\text{ then H}_2\text{O}]{\text{Na in}} C_6H_5CH_3 + \underset{\text{I}}{HOCH_2CH(OR)_2}$$

VIa, X = Br, R = C_2H_5; VIIa, R = C_2H_5

VIb, X = Cl, R = CH_3; VIIb, R = CH_3

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(1) This work was supported by the Office of Ordnance Research, Contract No. D.A.-11-022-ORD-1716.

(2) W. E. Parham, H. Wynberg and F. L. Ramp, THIS JOURNAL, **75**, 2065 (1953).

(3) (a) A. Pinner, *Ber.*, **5**, 147 (1872). (b) W. H. Hartung and H. Adkins, THIS JOURNAL, **49**, 2520 (1927); F. Beyerstedt and S. M. McElvain, *ibid.*, **58**, 529 (1936); F. Krausz, *Ann. chim.*, [12], **4**, 811 (1949).

Cyclization of the acetals I by acetal interchange was accomplished in dry ether in the presence of catalytic amounts of sulfuric acid. These compounds[4] have been prepared previously by Bergmann and Miekeley,[5] and by Fisher and Taube[6] by different methods, but in each case only one of the two possible geometrical isomers was reported. The dialkoxydioxanes II obtained in this work appeared to be a mixture of these isomers, as indicated by the composition of fractions with different melting points.

The cyclic acetals II were dialkoxylated by a vapor phase reaction employing alumina, and the monoölefins, 5-ethoxy-1,4-dioxene-2 (IIIa) and 5-methoxy-1,4-dioxene-2 (IIIb) were obtained in yields of 41–68%. The structures of these products were established by their conversion into glyoxal osazone, and by their reduction to the corresponding alkoxydioxanes.[7] Although a number of dealkoxylation experiments were performed (under mild to drastic conditions yielding varying amounts of alkoxydioxenes) the presence of 1,4-dioxadiene in the effluents could not be demonstrated. Thus, the ultraviolet spectra of various fractions of the low boiling effluents showed extremely little absorption and no peak at 250 mμ, at which wave length 1,4-dioxadiene has an extinction coefficient of 5,000.[8]

Experimental

Benzyloxyacetaldehyde Diethyl Acetal (VIIa).—A modification of the method of Rotbart[9] was used. Sodium benzyloxide was prepared by solution of sodium (28 g., 1.21 gram-atoms) in dry benzyl alcohol (200 g., 1.85 moles). To this well-stirred solution was added a mixture of bromoacetal (197 g., 1.0 mole) in dry toluene (150 ml.). The resulting mixture was refluxed for five hours, cooled and precipitated sodium bromide was removed by filtration. The filtrate was washed with water, dried over anhydrous potassium carbonate and then fractionated at reduced pressure. The product VIIa weighed 183 g. (82% yield), b.p. 99–100° (0.55 mm.), n^{25}D 1.4770.

Benzyloxyacetaldehyde Dimethyl Acetatal (VIIb).—The same procedure was used for the preparation of this compound from sodium benzyloxide and chloroacetaldehyde dimethyl acetal, except that the time of reflux was extended to 16 hours. From 187 g. (1.5 moles) of the chloroacetal there was obtained 222.5 g. (75.7% yield) of VIIb, b.p. 134.5–135.5° (15 mm.), n^{25}D 1.4873.

Hydroxyacetaldehyde Diethyl Acetal (Ia).—To a stirred mixture of 152 g. (0.68 mole) of VIIa, 450 ml. of dry ether and 900 ml. of liquid ammonia were added small pieces of sodium until the typical blue color of sodium in liquid ammonia persisted for 30 minutes. A total of 26 g. (1.13 gram-atoms) of the metal was required. Excess sodium was destroyed by the addition of absolute ethanol, and, after evaporation of ammonia, water was added with stirring to decompose the sodium salt of hydroxyacetal. The resulting ethereal mixture was washed twice with water, the washes combined, and the alkaline solution saturated first with carbon dioxide and then with sodium carbonate. The solution was extracted twice with ether, and the combined ethereal solutions were dried over anhydrous potassium carbonate. Ether was distilled from the dried solution, and the residue was fractionated at reduced pressure. The fraction boiling at 69–73° (11 mm.) was collected. Redistillation of this fraction afforded 76 g. (81% yield) of Ia, b.p. 69–70.5° (10 mm.), n^{25}D 1.4145.

Anal. Calcd. for $C_6H_{14}O_3$: C, 53.71; H, 10.52. Found: C, 53.30; H, 10.69.

The methone derivative of the hydrolyzed acetal was prepared according to the procedure of Vörlander,[10] and crystals melting at 237–238.5° were obtained. Vörlander reported the melting point of this derivative to be 237.5°.

Hydroxyacetaldehyde Dimethyl Acetal (Ib).—The same procedure as that described above was used except that the aqueous washes were countercurrently extracted with ether for four days. From 425 g. (2.16 moles) of VIIb there was obtained 133 g. (58% yield) of product boiling at 58–60° (12 mm.), n^{25}D 1.4118.

Anal. Calcd. for $C_4H_{10}O_3$: C, 45.27; H, 9.50. Found: C, 45.42; H, 9.78.

2,5-Diethoxy-1,4-dioxane (IIa).—A solution of 50 g. (0.37 mole) of Ia in 150 ml. of dry ether, to which four drops of 96% sulfuric acid had been added, was refluxed for four hours and then allowed to stand overnight. A mixture of 1 g. of barium carbonate and 1 g. of anhydrous potassium carbonate was added and the mixture was stirred for one hour, after which time an acid reaction with moist alkacid paper was not shown. Solids were removed from the mixture by filtration through glass wool, and the filtrate was concentrated by distillation of ether. The residue was distilled under vacuum and the fraction boiling at 80–85° (11 mm.) was collected. This material was redistilled, and two fractions were collected:

Fraction 1, b.p. 85–86° (11 mm.), n^{25}D 1.4262, was liquid at room temperature. *Anal.* Calcd. for $C_8H_{16}O_4$: C, 54.53; H, 9.15. Found: C, 54.43; H, 8.97.

Fraction 2, b.p. 86° (11 mm.), n^{25}D 1.4268, was semisolid at room temperature. The solid was removed by filtration and recrystallized from petroleum ether to give colorless leaflets melting at 58.5–59°. *Anal.* Found: C, 54.19; H, 9.32. Physical constants for this isomer, as reported by Bergmann and Miekeley,[5a] are: b.p. 90° (12 mm.), n^{20}D 1.4293 (under cooled melt), m.p. 59–60°.

The weight of the combined fractions was 28.3 g. (87% yield).

2,5-Dimethoxy-1,4-dioxane (IIb).—The same procedure as that described above was used in the preparation of this compound. From 130 g. (1.22 moles) of Ib there was obtained 55.5 g. (61.2% yield) of IIb, semi-solid at room temperature. Crystallization of the solid from petroleum ether afforded colorless leaflets melting at 71.5–73°, b.p. 64–66° (12 mm.), n^{25}D 1.4269.

Anal. Calcd. for $C_6H_{12}O_4$: C, 48.64; H, 8.16. Found: C, 48.97; H, 8.47.

The melting point of this compound has been reported by Bergmann and Miekeley[5b] as 72°.

5-Ethoxy-1,4-dioxene-2 (IIIa).—A glass column, 10 inches long and 0.75 inch in diameter, filled with $^1/_8$ inch Harshaw alumina pellets, was conditioned for 16 hours at 375°. The temperature was then lowered to 300°, and 50 ml. of dry ethanol was passed through the column with a nitrogen flow rate of 0.5 l./min. A water-cooled condenser and a receiver containing 0.5 g. of anhydrous potassium carbonate was attached to the column, and 73 g. (0.42 mole) of a mixture of the *cis* and *trans* isomer of IIa was passed through the column at a rate of 3 drops per minute and a nitrogen flow rate of 0.5 l./min. The dark yellow effluent was fractionated at reduced pressure, and the fraction boiling at 47–49° (14 mm.) was collected. Refractionation of this material afforded 26.5 g. (41% yield) of IIIa, b.p. 61° (27 mm.), n^{25}D 1.4341.

Anal. Calcd. for $C_6H_{10}O_3$: C, 55.37; H, 7.75. Found: C, 55.30; H, 7.84.

Glyoxal Osazone.—A mixture of 1 g. of IIIa and 20 ml. of 5% hydrochloric acid was heated on the steam-bath for one hour and then added to a solution of 9 g. of freshly distilled phenylhydrazine in 70 ml. of 5% acetic acid. The solution was warmed on the steam-bath for 48 hours and then cooled, whereupon dark yellow crystals (2.4 g., 66% yield) separated. Recrystallization of this solid from aqueous ethanol was accomplished, with little loss of material, to give light yellow crystals melting at 166.5–168.5°.

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(4) See R. K. Summerbell and L. K. Rochen, THIS JOURNAL, **63**, 3241 (1941). These workers offered the first experimental evidence that the glycol–aldehyde dimer series of compounds really had a dioxane structure.

(5) (a) M. Bergmann and A. Miekeley, *Ber.*, **54**, 2155 (1921); **62**, 2298 (1929); (b) **64**, 802 (1931).

(6) H. O. L. Fisher and C. Taube, *ibid.*, **60**, 1708 (1927).

(7) W. E. Parham, THIS JOURNAL, **69**, 2449 (1947).

(8) L. W. Pickett and E. L. Sheffield, *ibid.*, **68**, 216 (1946).

(9) M. Rotbart, *Compt. rend.*, **197**, 1225 (1933).

(10) D. Vörlander, *Z. anal. Chem.*, **77**, 241 (1929).

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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[11] R. K. Summerbell and R. R. Umhoefer, THIS JOURNAL, **61**, 3020 (1939).

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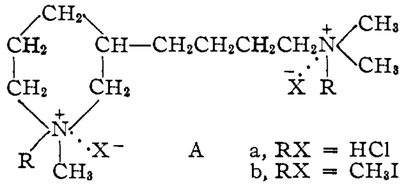
Synthetic Hypotensive Agents. III. Some 4,4′-Bipiperidines

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

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[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).