nium salts, derived from these bis-tertiary amines, were found to be very potent ganglionic blockers. The potency of certain of the quaternary salts exceeded that of hexamethonium considerably, as already reported by Libman, *et al.*[6,7]

Acknowledgment.—The author is indebted to S. W. Blackman for the microanalyses included and to Drs. S. Norton and K. Colville for the pharmacological results summarized here.

Experimental

Preparation of the Diamines.—A solution containing 0.1 mole of 1,6-hexamethylene dibromide and 0.4 mole of the secondary amine in 100 cc. of methanol was refluxed for 18 hours. The reaction mixture was evaporated *in vacuo* to remove solvent and unreacted amine. The residue was treated with 20% aqueous alkali, the product was taken up in ether; the ether layer, after drying over anhydrous sodium sulfate, was evaporated. The pure bis-amine was obtained by vacuum distillation and was then converted into the hydrochloride and certain quaternary salts.

The quaternary salts were obtained by refluxing of the bis-tertiary amines with methyl or ethyl iodide in methanol.

Details for all compounds are included in Table I.

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Preparation and Derivatives of Cyano-1,4-dioxane

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The literature contains numerous references to the formation of α-cyanoethers from α-chloroethers.[1] This paper reports the preparation of cyano-1,4-dioxane from chloro-1,4-dioxane, using a variety of conditions. The variables included the kind of solvent (ethyl ether, isopropyl ether, 1,4-dioxane, acetone, *o*-dichlorobenzene, toluene, glacial acetic acid), time of reaction (three hours to several days), temperature (0° to the boiling point of the solvent), and the kind of metal cyanide (zinc, mercuric, cuprous and silver). The use of cuprous cyanide in boiling benzene for four hours gave less than a 10% yield. The best yield (42%) was realized by using silver cyanide in boiling toluene for four hours. No isocyanide was formed since treatment with mercuric oxide gave a negative test, and reduction gave a primary amine by the Hinsberg test.

Hydrolysis of cyano-1,4-dioxane gave the expected carboxylic acid. Attempts to prepare benzoyl-1,4-dioxane by addition of the nitrile to phenylmagnesium bromide were unsuccessful, the yellow viscous product containing no nitrogen but giving a negative ketone test with 2,4-dinitrophenylhydrazine. Benzoyl-1,4-dioxane was prepared, however, by adding phenylmagnesium bromide to the nitrile (inverse Grignard).

Attempts to reduce cyano-1,4-dioxane to aminomethyl-1,4-dioxane with sodium and alcohol or moist ether were unsuccessful. Reduction with lithium aluminum hydride gave the aminomethyl derivative in poor yield (42%).

The reaction of aminomethyl-1,4-dioxane with *p*-acetamidobenzenesulfonyl chloride gave N-(2-dioxanylmethyl)-4-aminobenzenesulfonamide which was tested for physiological activity by Sharp and Dohme, Inc., Philadelphia. It was found to be inactive *in vitro* toward *Proteus vulgaris*, and *in vivo* toward a strain of hemolytic streptococcus.

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Experimental

Cyano-1,4-dioxane.—A solution of chloro-1,4-dioxane was prepared by passing 9.1 g. (0.25 mole) of dry hydrogen chloride into 22.0 g. (0.25 mole) of 1,4-dioxene in 40 ml. of dry toluene.[2] If the addition of hydrogen chloride is too rapid, a tar results. The chlorodioxane solution was added dropwise with vigorous stirring to 33.7 g. (0.25 mole) of silver cyanide suspended in 125 ml. of dry toluene. An intermediate sticky mass broke up after half an hour and the mixture was then refluxed for four hours. The silver chloride was removed by filtration, the toluene by distillation and the residue fractionated under reduced pressure. Cyano-1,4-dioxane is a pleasant smelling liquid, somewhat soluble in water; yield 12.0 g. (42%), b.p. 98° (20 mm.), n^{20}_{D} 1.4493, d^{20}_{4} 1.1474.

Anal. Calcd. for $C_5H_7O_2N$: C, 53.09; H, 6.23; *MR*, 26.12. Found: C, 52.70; H, 6.18; *MR*, 26.43.

1,4-Dioxanecarboxylic Acid.—A solution of 5.0 g. (0.12 mole) of sodium hydroxide in 45 ml. of distilled water was added to 6.5 g. (0.057 mole) of cyano-1,4-dioxane in a 200-ml. r.b. flask. When warmed, the contents liberated ammonia and turned pale yellow. The mixture was refluxed for four hours, acidified with 15 ml. of 6 *N* sulfuric acid and extracted with three 30-ml. portions of ether. The water solution was evaporated at low pressure and extracted with several 25-ml. portions of ether. The ether solution, dried over anhydrous sodium sulfate, was evaporated, leaving an oil which crystallized when chilled. Recrystallization from carbon tetrachloride gave 3.5 g. (46%) of crystals melting at 83.5–85°.

Anal. Calcd. for $C_5H_8O_4$: C, 45.45; H, 6.10; neut. equiv., 132.1. Found: C, 45.31; H, 6.11; neut. equiv., 132.6.

A water solution of the acid turns blue litmus red and tastes like citric acid. The calculated ionization constant at 25°, based on the Beckman *p*H measurement of 0.1 to 0.2 *M* solutions of the acid in doubly distilled water, is about 7×10^{-4}. The calculation was made on the assumption that the acid is monocarboxylic.

Benzoyl-1,4-dioxane.—A phenylmagnesium bromide solution, prepared from 15.7 g. (0.1 mole) of bromobenzene and 2.4 g. (0.1 mole) of magnesium in 75 ml. of ether, was added dropwise to a stirred and cooled solution of 5.7 g. (0.05 mole) of cyano-1,4-dioxane in 40 ml. of ether until no further reaction was visible (about two-thirds of the Grignard solution was used). After standing overnight, the mixture was added to 50 g. of crushed ice and 10 ml. of 6 *N* hydrochloric acid. The ether layer was separated, the water layer extracted with three 10-ml. portions of ether, and the combined ether solution dried over anhydrous sodium sulfate. Removal of the ether and fractionation of the residual oil under reduced pressure gave 7.2 g. of a light yellow viscous liquid boiling at 172–182° (25 mm.). Redistillation gave 6.1 g. (64%) of a colorless, water-insoluble, viscous liquid boiling at 182–183.5° (25 mm.), n^{20}_{D} 1.5487, d^{20}_{4} 1.1915.

Anal.[3] Calcd. for $C_{11}H_{12}O_3$: C, 68.75; H, 6.22; *MR*, 50.49. Found: C, 68.45; H, 6.38; *MR*, 50.86.

The 2,4-dinitrophenylhydrazone of benzoyl-1,4-dioxane melts at 153–154° with darkening.

Anal.[3] Calcd. for $C_{17}H_{16}O_6N_4$: N, 15.05. Found: N, 14.43.

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(1) M. D. Gauthier, *Compt. rend.*, **143**, 831 (1906); H. R. Henze and J. H. Clark, *J. Org. Chem.*, **2**, 508 (1938); S. P. Lingo and H. R. Henze, THIS JOURNAL, **61**, 1574 (1939); H. R. Henze, G. W. Benz and G. L. Sutherland, *ibid.*, **71**, 2122 (1949); W. Baker and A. Shannon, *J. Chem. Soc.*, 1598 (1933); F. P. Tellegen, "Dioxan en Derivaten," Technical University, Delft, Holland, 1934, pp. 75–87; H. R. Henze and T. R. Thompson, THIS JOURNAL, **65**, 1422 (1943).

(2) R. K. Summerbell and L. N. Bauer, *ibid.*, **57**, 2364 (1935).

(3) Analysis by Micro-Tech Laboratories, Skokie, Ill.

Aminomethyl-1,4-dioxane.—A modified procedure of Amundsen and Nelson[4] was used; 7.6 g. (0.2 mole) of lithium aluminum hydride was crushed under dry ether and refluxed with stirring in 400 ml. of dry ether for two hours. After cooling the mixture to 0°, 22.6 g. (0.2 mole) of cyano-1,4-dioxane in 40 ml. of dry ether was added dropwise over 0.5 hour. After an additional 0.5 hour, 8 ml. of water was added, then 6 ml. of 6 *N* sodium hydroxide, and finally 28 ml. of water. The ether solution was decanted into a fluted filter, the residual salts refluxed briefly with two 100-ml. portions of ether, and the combined ether solution dried over anhydrous sodium sulfate. Removal of the ether and fractionation of the residual oil under reduced pressure gave 9.9 g. (42%) of a colorless water-soluble liquid with a strong ammonia odor, boiling at 84° (18 mm.), n^{20}_D 1.4660, d^{20}_4 1.0798.

Anal. Calcd. for $C_5H_{11}O_2N$: C, 51.26; H, 9.45; *MR*, 29.80. Found: C, 51.03; H, 9.78; *MR*, 30.02.

The product reacted with benzenesulfonyl chloride (Hinsberg test), giving N-(dioxanylmethyl)-benzenesulfonamide. The amide melted at 77–78° and crystallized as needles from alcohol.

Anal. Calcd. for $C_{11}H_{15}O_4NS$: N, 5.45. Found: N, 5.39.

N-(Dioxanylmethyl)-4-aminobenzenesulfonamide.—19.8 g. (0.085 mole) of *p*-acetamidobenzenesulfonyl chloride was added slowly to a solution of 9.9 g. (0.085 mole) of aminomethyl-1,4-dioxane in 13.6 g. (0.17 mole) of anhydrous pyridine. The mixture, heated at 100° for one hour and then poured into 85 ml. of water acidified with hydrochloric acid, gave 18.6 g. of crude product melting at 72–73° after crystallization from water. The material was refluxed for 1.5 hours with 100 ml. of 2 *N* sodium hydroxide, filtered, and the filtrate neutralized with concentrated hydrochloric acid. Upon cooling, the oil gave a yellow solid which was crystallized from 500 ml. of hot water containing decolorizing charcoal. The product, separating as fine white flakes, weighed 10 g. (43%), melted at 98–101° (but not to a clear liquid) and decomposed at 205°.

Anal. Calcd. for $C_{11}H_{16}O_4N_2S$: C, 48.53; H, 5.93; S, 11.77. Found: C, 48.60; H, 6.07; S, 11.82.

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[4] L. H. Amundsen and L. S. Nelson, THIS JOURNAL, **73**, 242 (1951).

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Synthesis of 2-Methyl-5-*t*-butylacylbenzenes

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During the course of the present investigation, it was shown by Taylor and Watts[2] that direct Friedel–Crafts acetylation of *p*-*t*-butyltoluene leads to a rearranged product, probably 2-methyl-4-*t*-butylacetophenone. This has been confirmed in our own experience, and we have demonstrated that the use of a low reaction temperature does not prevent the rearrangement. Acetylation of *p*-*t*-butyltoluene with acetyl chloride and aluminum chloride in carbon disulfide at −20 to −30° led to the formation of an acyl derivative in 57% yield. This acyl derivative gave a semicarbazone melting at 197°, while the semicarbazone of 2-methyl-5-*t*-butylacetophenone (prepared as described below) melts at 183°; a mixture of the two semicarbazones melted at 156–160°. Taylor and Watts also report[2] a melting point of 197° for the semicarbazone of their acetyl derivative of *p*-*t*-butyltoluene. Hence, other methods were investigated for the synthesis of pure 2-methyl-5-*t*-butylacylbenzenes.

Chloromethylation of *t*-butylbenzene gave *p*-*t*-butylbenzyl chloride in 70% yield. Reaction of the Grignard reagent from *p*-*t*-butylbenzyl chloride with acetic anhydride gave[3] 2-methyl-5-*t*-butylacetophenone in 19% yield. This product gave a semicarbazone, m.p. 183°, which did not depress the m.p. of the semicarbazone of authentic 2-methyl-5-*t*-butylacetophenone prepared as described below; it did, however, markedly depress the m.p. of the semicarbazone of the product of direct actylation of *p*-*t*-butyltoluene. The reaction of *p*-*t*-butylbenzylmagnesium chloride with acetic anhydride also led to the formation of 12% of a second unidentified ketone, m.p. of semicarbazone 144–145°, and a small amount of 1,2-di-(*p*-*t*-butylphenyl)-ethane, m.p. 149°. This latter product was produced in 57% yield by coupling *p*-*t*-butylbenzylmagnesium chloride in the presence of silver bromide according to the procedure of Gardner and Borgstrom.[4]

Bromination of *p*-*t*-butyltoluene in the presence of iodine as catalyst gave 2-methyl-5-*t*-butylbromobenzene in 73% yield.[2] Carbonation of the Grignard reagent of this halide gave 2-methyl-5-*t*-butylbenzoic acid, m.p. 98°.[5] Reaction of 2-methyl-5-*t*-butylphenylmagnesium bromide with acetic anhydride at −35 to −50° according to the procedure of Newman and Booth[6] gave 2-methyl-5-*t*-butylacetophenone in 36% yield. The structure of this product was proved by hypohalite oxidation to the known[5] 2-methyl-5-*t*-butylbenzoic acid, m.p. 98°; the ketone gave a semicarbazone, m.p. 183°, identical with that of the product of reaction of *p*-*t*-butylbenzylmagnesium chloride with acetic anhydride. A more satisfactory and convenient procedure for the preparation of 2-methyl-5-*t*-butylacetophenone proved to be the organocadmium procedure of Gilman and Nelson.[7] 2-Methyl-5-*t*-butylphenylmagnesium bromide was converted to the corresponding organocadmium reagent and caused to react with the appropriate acyl halide to give the series of 2-methyl-5-*t*-butylacylbenzenes reported in Table I.

Experimental[8]

Chloromethylation of *t*-Butylbenzene.[9]—*t*-Butylbenzene, 134 g. (1 mole), was mixed with 120 g. of formalin, 36 g. of concd. hydrochloric acid, 68 g. (0.5 mole) of anhydrous zinc chloride and 10 g. of trioxymethylene. Dry hydrogen chloride was bubbled into the mixture with stirring; a temp. of 75–82° was maintained during a reaction period of 27 hours. The reaction mixture was poured into 500 ml. of ice-water, the organic layer was separated, and the aqueous layer extracted five times with 50-ml. portions of ether. The ether extracts and organic layer were combined and washed successively with cold water, 5% aqueous sodium carbonate solution, and again with cold water. The ethereal solution was dried over anhydrous sodium sulfate, the ether was distilled off, and the residue was distilled to give

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[1] Abstracted from a thesis presented by R. N. Prasad to the Graduate Faculty of Emory University in partial fulfillment of the requirements for the degree of Doctor of Philosophy, June, 1954.

[2] E. P. Taylor and G. E. Watts, *J. Chem. Soc.*, 1123 (1952).

[3] Compare P. R. Austin and J. R. Johnson, THIS JOURNAL, **54**, 647 (1932) for similar reactions of benzylmagnesium chloride.

[4] J. H. Gardner and P. Borgstrom, *ibid.*, **51**, 3375 (1929).

[5] Taylor and Watts, ref. 2, report 101° as the m.p. of this acid; we were unable to raise our m.p. by repeated crystallizations.

[6] M. S. Newman and H. T. Booth, Jr., THIS JOURNAL, **67**, 154 (1945).

[7] H. Gilman and J. F. Nelson, *Rec. trav. chim.*, **55**, 518 (1936).

[8] M.p.'s were determined in capillary tubes and are uncorrected.

[9] *Cf.*, A. Levy and C. Darzens, *Compt. rend.*, **199**, 1426 (1934); R. Berg, *Roczniki Chem.*, **14**, 1249 (1934); G. S. Skinner, J. A. Gladner and R. F. Heitmiller, THIS JOURNAL, **73**, 2230 (1951).