The ester was obtained in 70% yield by the addition of one mole of potassium *t*-butoxide (prepared under nitrogen from 39 g. of potassium metal in 800 ml. of *t*-butyl alcohol) to a mixture of one mole (307 g.) of ethyl α-bromolaurate and one mole (58 g.) of acetone, according to the method reported by Johnson, *et al.*[6]

In order to determine if the glycidic ester would rearrange on being subjected to high temperatures, a 8.9-g. sample was heated to 280–290° for two hours. Distillation after this treatment gave 7.2 g. of material boiling at 168° (4 mm.) and having a refractive index of 1.4431.

Saponification of Ethyl α-*n*-Decyl-β,β-dimethylglycidate. A sample of the ester was added to 1.5 times the equivalent amount of potassium hydroxide in diethylene glycol and the mixture refluxed for one hour. The cooled mixture was then poured into a slurry of concentrated hydrochloric acid and ice and immediately extracted with ether. The ether layer was washed with water, dried over anhydrous sodium sulfate and the ether removed by means of a steam-bath. The crude glycidic acid was a viscous oil which could not be obtained in a crystalline form.

Another sample of the ester was added to one equivalent of sodium ethoxide in excess ethanol. The cooled (ice-bath) mixture was then treated with exactly one equivalent of water and stirred for one hour. The mixture was poured into a concentrated hydrochloric acid–ice slurry whereupon a solid was formed. The mixture was extracted immediately with ether. The ether solution was washed, dried and the ether removed, leaving a solid acid which melted at 43–47°. Attempts to recrystallize the material gave only oils. On standing overnight the solid changed to a viscous liquid which could not be induced to crystallize. A 68% yield of ketone was formed by decarboxylating the glycidic acid obtained by the sodium ethoxide (Claisen method) saponification, whereas only a 42% yield of ketone was obtained from the decarboxylation of the saponification product where potassium hydroxide was employed. It would appear that the Claisen saponification yields a purer product than that obtained through the use of potassium hydroxide.

Since Darzens saponified this ester by the use of potassium hydroxide dissolved in ethanol, his procedure was repeated. The viscous acid so obtained decarboxylated smoothly to give a 42% yield of the ketone.

Decarboxylation of α-*n*-Decyl-β,β-dimethylglycidic Acid.—Thermal decarboxylation of samples of this acid following a previously reported[2] method gave yields varying from 42–69% depending upon the method used to saponify the glycidic ester. Fractionation (Todd assembly) of the mixtures after decarboxylation was complete gave a product with b.p. 133° (4 mm.), $n^{20}D$ 1.4357, d^{20}_4 0.8314, d^0_4 0.8443.

Anal. Calcd. for $C_{14}H_{28}O$: C, 79.24; H, 13.21; *MR*, 67.01. Found: C, 79.80; H, 13.22; *MR*, 67.22.

The material formed a 2,4-dinitrophenylhydrazone (yellow platelets) which melted at 32.5° after three recrystallizations from ethanol.

Anal. Calcd. for $C_{20}H_{32}O_4N_4$: N, 14.27. Found: N, 14.21.

It also formed a semicarbazone (84% yield based on ketone) which melted at 72.5–73° after three recrystallizations. Darzens[3] reported that his decarboxylation product boiled at 156–160° (18 mm.) and formed a semicarbazone which melted at 59.5°.

An authentic sample of 2-methyl-3-tridecanone was prepared from 0.25 mole of di-*n*-decylcadmium and 0.5 mole of isobutyryl chloride by the dialkylcadmium ketone synthesis. A detailed procedure has been given in an earlier report.[8] This material formed a 2,4-dinitrophenylhydrazone which melted at 32° and a semicarbazone which had a melting point of 72–73°. Mixed melting points of the similar derivatives from the authentic sample of ketone and the decarboxylation product showed no depression.

Although the decarboxylation product seemed pure, the material reduced Tollens reagent and decolorized a 1% permanganate solution. A sample of the material therefore was subjected to oxidation with aqueous potassium permanganate according to the method of Shriner and Fuson.[9] Less than 10% of the material was oxidized. The same results were obtained when a sample was dissolved in acetone and subjected to the oxidation. The presence of oxidizable material in the ketone probably accounts for Darzens' conclusion that the decarboxylation product was an aldehyde.

Johnson, *et al.*,[6] recently have reported a modification of Yarnall and Wallis' method of decarboxylating glycidic acids which involves the preparation of the α-chloro-β-hydroxy acid by treating the sodium salt of a glycidic acid with anhydrous HCl. The addition of a base causes the chlorohydroxy acid to decarboxylate. Use of this method with the sodium salt obtained by Claisen's method of saponification gave a 63% yield of 2-methyl-3-tridecanone (isolated as the 2,4-dinitrophenylhydrazone).

Attempted Preparation of Ethyl α-*n*-Decyl-β-methyl-β-phenylglycidate.—Although Darzens, using the α-chloro ester, reported no difficulty in obtaining the compound, we have not been able to obtain a product which could be shown to be the desired ester, using ethyl α-bromolaurate as starting material. Two attempts were made using sodium ethoxide as the condensing agent, but attempted distillation of the reaction products caused decomposition and the formation of undistillable tars. Four attempts were made to prepare the ester using potassium *t*-butoxide as the condensing agent. From the first three of these preparations no material was obtained which could be identified as the glycidic ester. The last preparation, in which the reaction mixture was allowed to stand overnight and was then heated for 2.5 hours on a steam-bath, gave 17 g. (10% yield if considered to be the glycidic ester) of a product with b.p. 205° (4 mm.), $n^{20}D$ 1.4853, d^{20}_4 0.9631. Darzens[3] reports b.p. 185–190° (5 mm.), $n^{20}D$ 1.4713, d^0_0 0.993.

Anal. Calcd. for $C_{22}H_{34}O_3$: C, 76.30; H, 9.83; *MR*, 102.53; mol. wt., 346. Found: C, 76.74; H, 9.86; *MR*, 103.01; mol. wt., 317, 321.

Although the analysis might indicate the expected glycidic ester, the molecular weight discrepancy and the following information leaves some doubt as to the nature of the product. A gas was evolved when a sample of the ester was saponified. No carbonyl derivative or acid derivative could be obtained from the acidified saponification mixture. The original reaction product decolorized a solution of bromine in carbon tetrachloride. In view of the possible rearrangement to the α-keto ester during the distillation, an attempt was made to obtain a 2,4-dinitrophenylhydrazone from the original reaction product but no derivative could be isolated. The material has not been identified conclusively.

Atomic refractivity values were taken from those given by Vogel.[10] Melting points are uncorrected. Analyses were made by the Oakwold Laboratories, Alexandria, Va. The infrared absorption curve of ethyl α-*n*-decyl-β,β-dimethylglycidate has been recorded by S. P. Sadtler Research Laboratories, 1517 Vine St., Philadelphia 3, Pa.

Acknowledgment.—We wish to express our appreciation for the financial aid given us by the Coe Research Fund and by a Frederick Gardner Cottrell research grant from Research Corporation.

(8) N. K. Nelson and H. H. Morris, THIS JOURNAL, **75**, 3337 (1953).

(9) R. L. Shriner and R. C. Fuson, "Identification of Organic Compounds," 3rd Ed., John Wiley and Sons, Inc., New York, N. Y.

(10) A. I. Vogel, "A Textbook of Practical Organic Chemistry Including Qualitative Analysis," 2nd Ed., Longmans, Green and Co., New York, N. Y.

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Synthetic Hypotensive Agents. II. Some Hexamethylene-1,6-bis-*t*-amines and Bis-quaternary Salts as Ganglionic Blocking Agents

BY ARTHUR P. PHILLIPS

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An earlier study resulted in the discovery[1,2] of potent ganglionic blocking activity in a series of bis-tertiary amines, of structure I, as well as in their bis-quaternary ammonium salts. These compounds are believed to represent the first reported examples

(1) S. Norton and A. P. Phillips, *Nature*, **172**, 867 (1953).

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

TABLE I

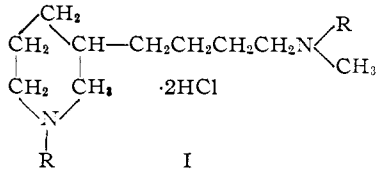
1,6-BIS-*t*-AMINOHEXANES AND DERIVATIVES

$$R_2\overset{+}{N}-(CH_2)_6-\overset{+}{N}R_2$$
$$R' \quad X^- \qquad X^- \quad R'$$

R_2N	R'X	M.p., °C.[a]	Formula	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found
Dimethylamino	HCl	245–246[b]	$C_{10}H_{26}N_2Cl_2$	49.0	49.3	10.7	10.4
Pyrrolidino	HCl	238–239[c,d,e]	$C_{14}H_{30}N_2Cl_2$	56.6	56.4	10.2	10.0
Pyrrolidino	C_2H_5I	245–246[f]	$C_{18}H_{38}N_2I_2$	40.3	40.4	7.2	7.3
Piperidino	HCl	263–264[g,h]	$C_{16}H_{34}N_2Cl_2$	59.1	59.1	10.5	10.4
Piperidino	C_2H_5I	248–249	$C_{20}H_{42}N_2I_2$	42.6	42.6	7.5	7.4
Morpholino	HCl	255–256[i]	$C_{14}H_{30}N_2O_2Cl_2\cdot H_2O$	48.4	48.4	9.3	9.4
Isoquinolino	Br	219–221	$C_{24}H_{26}N_2Br_2$	57.3	57.3	5.2	5.4
Tetrahydroisoquinolino	HCl	272–273	$C_{24}H_{34}N_2Cl_2$	68.4	68.1	8.1	7.9
Tetrahydroisoquinolino	CH_3I	228–229	$C_{26}H_{38}N_2I_2$	49.3	49.1	6.1	6.4
Dimethylamino	CH_3Br	>320[j]	$C_{14}H_{26}N_2Br_2$	44.0	44.3	6.8	6.6

[a] Melting points are uncorrected. Yields of the products were usually above 85%; the products were purified by several recrystallizations from mixtures of methanol and ethyl acetate or ether. [b] The base boiled at 206–208° at atmospheric pressure. This base had been described by V. Prelog, *Collection Czechoslav. Chem. Communs.*, **2**, 712 (1930); through *C. A.*, **25**, 1218[2] (1931). He obtained it in poor yield as a by-product during electrolytic reduction of succinic acid monodimethylamide. [c] The base boiled at 148–149° at 4 mm. [d] Reported in reference 6 as a by-product in the reaction between tetramethylene dibromide and hexamethylenediamine. [e] The 1,6-bis-pyrrolidino-bis-methiodide melting at 182–183° was also described in reference 6. [f] Given in reference 6 as the bromide. [g] The base boiled at 165–167° at 4 mm. This base was also made by J. von Braun, *Ber.*, **43**, 2860 (1910). [h] The 1,6-bis-piperidino-bis-methiodide melting at 239–240° was also reported earlier by J. von Braun, *ibid.*, **43**, 2860 (1910). [i] The base boiled at 173–174 at 4 mm. and solidified to a solid which melted at 41–42°. This base was reported in reference 6 and also by W. R. Coleman and W. G. Bywater, THIS JOURNAL, **66**, 1821 (1944), and by G. W. Anderson and C. B. Pollard, *ibid.*, **61**, 3440 (1939). The 1,6-bis-morpholino-bis-methiodide melting at 217–218° and bis-ethiodide melting at 253–254° were also described in reference 6. [j] This compound has the structure $(CH_3)_3\overset{+}{N}CH_2$–C$_6H_4$–$CH_2\overset{+}{N}(CH_3)_3$ $2Br^-$.

of bis *tertiary amines* possessing ganglionic blocking potency, both intravenous and oral, equal to or surpassing that of the well-known hexamethonium salts.



I R = CH_3, C_2H_5, etc.

The structure of the products, I, bore a striking though inadvertent resemblance to the hexamethylene bis-ammonium series of compounds. It seemed desirable to exploit the new findings in several directions immediately.

One of the lines explored was that of incorporating certain of the structural features of both I and of hexamethonium into a different molecular arrangement. The first and possibly simplest scheme involved the preparation of a series of hexamethylene-1,6-bis-amines in which the amino constituents were heterocyclic by analogy with the piperidine ring of I. This first group was arbitrarily limited to hexamethylene derivatives since the hexamethonium salts have most recently found favor over their pentamethonium analogs in the treatment of hypertension. In deference to the interesting and novel di-tertiary amine feature of I, the di-tertiary amines were first made and submitted for test in each case. These di-tertiary amines were subsequently quaternized with methyl and ethyl iodide, and the resulting bis-ammonium compounds were also examined as possible hypotensive agents.

Following the recognition of strong autonomic ganglionic blocking activity in various polymethylene bis-ammonium salts[3,4] several papers have appeared introducing certain modifications in the end group structure.[5–7] Several of the compounds prepared by Libman and co-workers[6,7] were made quite independently in the work of this paper.

The compounds reported here were made by one method. An excess of secondary amine was refluxed in alcohol solution for some hours with hexamethylene dibromide. The resulting di-tertiary amines were purified and tested as their hydrochlorides. These di-tertiary amines were further diquaternized with methyl and ethyl iodides.

In one case a tertiary amine, isoquinoline, was reacted with the dibromide to give a diquaternary salt at once. This was hydrogenated, using Adams catalyst, to the bis-tetrahydroisoquinoline derivative, and the latter di-tertiary amine was then further diquaternized with methyl iodide.

Another variation employed α,α'-dibromo-*p*-xylene in place of the simple hexamethylene chain. In this case only the completely methylated bis-quaternary was prepared by reaction of the dibromide with trimethylamine.

Ganglionic blocking activity was found in several of the bis-tertiary amines of this series, although none was as potent as hexamethonium or as I (R = CH_3). The 1,6-bis-pyrrolidinohexane was about one fifth as potent as hexamethonium as a ganglionic blocking agent, while the 1,6-bis-piperidinohexane had about one-half the potency of its pyrrolidino analog. Several of the bis-quaternary ammo-

(3) R. B. Barlow and H. R. Ing, *Brit. J. Pharmacol.*, **3**, 298 (1948).
(4) W. D. M. Paton and E. J. Zaimis, *ibid.*, **4**, 381 (1949).
(5) R. Wien and D. F. J. Mason, *Brit. J. Pharmacol.*, **6**, 611 (1951).
(6) D. D. Libman, D. L. Pain and R. Slack, *J. Chem. Soc.*, 2305 (1952).
(7) R. Slack, D. D. Libman and D. L. Pain, U. S. Patent 2,667,493.

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.

Acknowledgment.—The authors wish to express their gratitude to the Research Corporation which made this work possible through a Frederick Gardner Cottrell grant.

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.

(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.