Bis(2,4,5-trichlorophenol)-piperazine Salt.—An anhydrous solution of 61 g. (0.71 mole) of piperazine in benzene was added to a warm solution of 280 g. (1.42 moles) of 2,4,5-trichlorophenol (m.p. 63.5–64.5°) in 500 ml. of benzene. The resulting solution was filtered, diluted with an equal volume of low-boiling petroleum ether, seeded and cooled. The colorless crystalline precipitate was collected by filtration, washed with petroleum ether and dried.

Synthetic Amebicides. VII. 6,6′-Diallyl-α,α′-bis(dialkylaminoalkylamino)-4,4′-bi-*o*-cresols[1]

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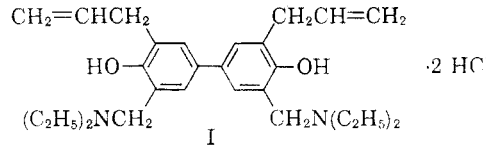
The antiamebic activity of biallylamicol[2,3] (I) in experimental[4,5]



I

and clinical[6,7] infections prompted us to synthesize other 6,6′-diallyl-α,α′-bis(amino-*o*-cresols) for antiparasitic evaluation. The present communication is concerned with the preparation of relatives of biallylamicol in which the diethylamino group is substituted with basic side chains similar to those found in antiamebic agents such as chloroquine, quinacrine, 4-(3-dibenzofuranyl)-1,1,7,7-tetraethyldiethylenetriamine (II),[8] and 1,1,7,7-tetraethyl-4-(3,5-xylyloxyphenyl)-diethylenetriamine (III).[8]

(1) For previous paper in this series, see E. F. Elslager and F. H. Tendick, *J. Med. Pharm. Chem.*, **5**, 546 (1962).

(2) J. H. Burckhalter, F. H. Tendick, E. M. Jones, W. F. Holcomb and A. L. Rawlins, *J. Am. Chem. Soc.*, **68**, 1894 (1946).

(3) The trade name for 6,6′-diallyl-α,α′-bis-(diethylamino)-4,4′-bi-*o*-cresol, dihydrochloride is Camoform.

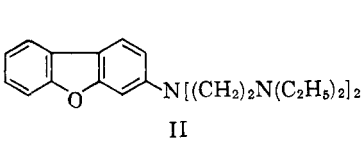
(4) For a description of test methods, see P. E. Thompson and J. W. Reinertson, *Am. J. Trop. Med.*, **31**, 707 (1951).

(5) P. E. Thompson, J. W. Reinertson, D. A. McCarthy, A. Bayles and A. R. Cook, *Antibiotics and Chemotherapy*, **8**, 433 (1955).

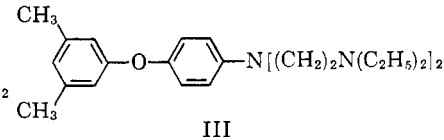
(6) H. Barrios, *Gastroenterol.*, **27**, 81 (1954).

(7) R. V. Taylor, *Am. J. Gastroenterol.*, **26**, 713 (1956), and references cited therein.

(8) F. Schönhöfer, "Chemotherapy, Fiat Review of German Science, 1939–1946," PB 85033, U. S. Dept. of Commerce, Office of Technical Services, Washington, D. C., 1948, p. 85; compound II known as Gavan, compound III as Gavano.

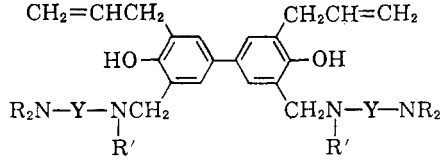


II



III

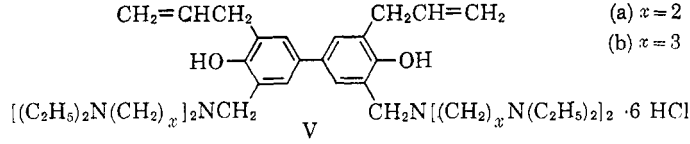
The condensation of 2,2′-diallyl-*p,p*′-biphenol with formaldehyde and N,N-diethyl-1,3-propanediamine, N^1,N^1-diethyl-1,4-pentanediamine, 1-(5-aminopentyl)piperidine and N,N-diethyl-N′-methyl-1,3-propanediamine in ethanol gave the corresponding 6,6′-diallyl-α,α'-bis(dialkylaminoalkylamino)-4,4′-bi-*o*-cresols (IVa through d) which



·4 HCL

(a) R′ = —H; Y = —$(CH_2)_3$—; NR_2 = —$N(C_2H_5)_2$
(b) R′ = —H; Y = —$CHCH_3(CH_2)_3$—; NR_2 = —$N(C_2H_5)_2$
(c) R′ = —H; Y = —$(CH_2)_5$—; NR_2 = —$N(CH_2)_5$
(d) R′ = —CH_3; Y = —$(CH_2)_3$—; NR_2 = —$N(C_2H_5)_2$

were isolated as the tetrahydrochloride salts. In like manner, two biallylamicol relatives of structure V were prepared from 2,2′-diallyl-



V

(a) $x=2$
(b) $x=3$

p,p′-biphenol, formaldehyde, 1,1,7,7-tetraethyldiethylenetriamine and 3,3′-bis(diethylamino)dipropylamine. As anticipated, the 6,6′-diallyl - α,α' - bis(dialkylaminoalkylamino) - 4,4′ - bi - *o* - cresol hydrochlorides were extremely hygroscopic and difficult to manipulate. Attempts to crystallize these amorphous, low-melting salts from a variety of organic solvents and solvent mixtures failed and purification was effected by solvent extraction and evaporation techniques.

1,1,7,7-Tetraethyldiethylenetriamine and 3,3′-bis(diethylamino)-dipropylamine, employed as starting materials for the preparation of Va and b, were prepared by the condensation of an ω-chloro-N,N-diethylalkylamine with a large excess of the appropriate N,N-diethylalkylenediamine in aqueous solution.

The 6,6′-diallyl-α,α'-bis(dialkylaminoalkylamino)-4,4′-bi-*o*-cresols

described herein were tested by P. E. Thompson and co-workers[9] of these laboratories against *Entamoeba histolytica in vitro*[5] and against intestinal amebiasis in rats.[10] The compounds were amebicidal *in vitro* at concentrations of 20 to 200 μg. ml. When administered in the diet to experimentally infected rats for a period of seven days, compounds IVa through c and Vb reduced the average degree of infection >50% at diet concentrations varying from 0.125 to 1.0%. None of the compounds was sufficiently more promising than biallylamicol to merit further study.

Acknowledgments.—The authors are indebted to Dr. Loren M. Long for advice and encouragement, and to Dr. Paul E. Thompson, Miss Anita Bayles and Dr. D. A. McCarthy for the biological testing. We also thank Mr. Charles E. Childs and associates for the microanalyses and Dr. J. M. Vandenbelt and associates for the determination of the infrared and ultraviolet absorption spectra.

Experimental[11]

1,1,7,7-Tetraethyldiethylenetriamine.—To a mixture of 581 g. (5 moles) of N,N-diethylethylenediamine,[12] 1 l. of water and 1 g. of copper powder was slowly added over a period of 1 hr. with vigorous mechanical stirring 172 g. (1 mole) of 2-chlorotriethylamine monohydrochloride[13]; 70 g. (0.5 mole) of anhydrous potassium carbonate was then added in one portion, and the mixture boiled under reflux for 5 hr. The cooled reaction mixture was made strongly alkaline with solid sodium hydroxide, extracted thoroughly with ether, and the combined ether extracts were dried over anhydrous potassium carbonate. The drying agent was collected by filtration, the ether was evaporated on a steam bath, and the residue distilled *in vacuo* through a 25-cm. Vigreux column to give 125 g. (58%) of the desired product as a colorless liquid, b.p. 115–116° (10 mm.), $n^{24}D$ 1.4466. The preparation of this base in crude form from N,N-diethylethylenediamine and 2-bromotriethylamine monohydrobromide in 35% yield has previously been reported[14]; the compound was characterized as the trihydrochloride salt.

Anal. Calcd. for $C_{12}H_{29}N_3$: C, 66.91; H, 13.58. Found: C, 66.44; H, 13.10.

3,3′-Bis(diethylamino)dipropylamine.—This amine was obtained in 97% yield from five moles of N,N-diethyl-1,3-propanediamine[15] and one mole of 3-chloro-N,N-diethylpropylamine monohydrochloride[13] as a colorless liquid, b.p. 140–142° (10 mm.), $n^{24}D$ 1.4522, according to the procedure cited above for the preparation of 1,1,7,7-tetraethyldiethylenetriamine.

(9) P. E. Thompson, A. Bayles and D. A. McCarthy, unpublished results.

(10) For a description of test methods, see P. E. Thompson, M. C. Dunn, A. Bayles and J. W. Reinertson, *Am. J. Trop. Med.*, **30**, 203 (1950).

(11) Melting points are uncorrected.

(12) Purchased from Carbide and Carbon Chemicals Company, New York 17, New York.

(13) Purchased from the Michigan Chemical Company, St. Louis, Michigan.

(14) L. J. Sacco, Jr., P. Z. Anthony, D. R. Borgen and L. G. Ginger, *J. Am. Chem. Soc.*, **76**, 303 (1954).

(15) Purchased from the American Cyanamid Company, New York 20, New York.

Anal. Calcd. for $C_{14}H_{33}N_3$: C, 69.07; H, 13.67. Found: C, 69.30; H, 13.59.

6,6′-Diallyl-α,α′-bis(3-diethylaminopropylamino)-4,4′-bi-*o*-cresol Tetrahydrochloride (IVa).—To a solution of 42.9 g. (0.33 mole) of N,N-diethyl-1,3-propanediamine[15] in 100 ml. of 95% ethanol was added 9 g. (0.30 mole) of paraformaldehyde. The mixture was warmed on the steam bath until solution occurred, and the solution was cooled to room temperature. This mixture was slowly added to a solution of 39.9 g. (0.15 mole) of 2,2′-diallyl-*p,p*′-biphenol in 100 ml. of ethanol with frequent shaking. The reaction was slightly exothermic. The mixture was allowed to stand at room temperature for 1 hr. and was then boiled under reflux for 2 hr. The ethanol was removed *in vacuo* on the steam bath, and the residue was dissolved in ether. After washing the ether solution thoroughly with 5% sodium hydroxide solution and water, the ether was removed *in vacuo*, the residue dissolved in ethanol and the ethanol solution treated with an excess of concentrated hydrochloric acid. Repeated addition and evaporation of methanol–benzene mixtures *in vacuo* on the steam bath yielded a pale yellow powder which was pulverized and dried *in vacuo* at 45° for 18 hr.; yield, 57.5 g. (55%), m.p. indefinite, beginning at 90–100°, foaming at 100°.

Anal. Calcd. for $C_{34}H_{54}N_4O_2 \cdot 4HCl$: N, 8.04. Found: N, 7.73.

6,6′-Diallyl-α,α′-bis(4-diethylamino-1-methylbutylamino)-4,4′-bi-*o*-cresol Tetrahydrochloride (IVb).—A mixture of 39.9 g. (0.15 mole) of 2,2′-diallyl-*p,p*′-biphenol, 50 g. (0.32 mole) of N^1,N^1-diethyl-1,4-pentanediamine and 200 ml. of 95% ethanol was stirred at room temperature while 23.6 ml. (0.32 mole) of 40% aqueous formaldehyde solution was added dropwise over a period of 20 min. The mixture was stirred for 30 min. without external heating and then stirred and boiled under reflux for 2 hr. The ethanol was removed on a steam bath and the residue was dissolved in ether. The ether solution was washed thoroughly with water, 10% sodium hydroxide solution, and water in that order, dried over anhydrous potassium carbonate and evaporated to an oil. The residue was treated with an excess of ethanolic hydrogen chloride, dissolved in a ethanol-methanol mixture, and diluted with acetone. The solvent was decanted from the waxy precipitate, and anhydrous ether was added to the residue. After repeated trituration with ether failed to cause the material to crystallize, the solid was collected by filtration, dissolved in water, made alkaline with sodium hydroxide and extracted with ether. The ether extracts were washed thoroughly with 10% sodium hydroxide solution and then with water. The ether solution was treated with decolorizing charcoal, dried over anhydrous potassium carbonate and the ether evaporated on the steam bath. The residue was treated with an excess of ethanolic hydrogen chloride, and the volatile materials removed *in vacuo* on the steam bath. The residue was dissolved in methanol and dried by repeated evaporations of benzene–methanol mixtures *in vacuo* on the steam bath. The frothy residue was pulverized and dried *in vacuo* at 45° for 20 hr.; yield 68 g. (60%) of a hygroscopic pale yellow powder, m.p. indefinite, 120–130° with foaming.

Anal. Calcd. for $C_{38}H_{62}N_4O_2 \cdot 4HCl$: C, 60.63; H, 8.84; N, 7.44. Found: C, 60.59; H, 8.45; N, 7.35.

6,6′-Diallyl-α,α′-bis(5-piperidinopentylamino)-4,4′-bi-*o*-cresol Tetrahydrochloride (IVc).—To a stirred mixture of 21.3 g. (0.08 mole) of 2,2′-diallyl-*p,p*′-biphenol, 28.5 g. (0.167 mole) of 1-(5-aminopentyl)piperidine[1] and 150 ml. of 95% ethanol was added dropwise, over a period of 30 min., 12.6 ml. (0.167 mole) of 40% aqueous formaldehyde solution. The mixture was stirred for 1 hr. and allowed to stand at room temperature for 18 hr. The mixture was stirred and

boiled under reflux for 2 hr. and the ethanol was removed on the steam bath. The cooled residue was dissolved in ether and the ether solution was washed successively with water, 10% sodium hydroxide solution and water. The ether solution was dried over anhydrous potassium carbonate, the drying agent was collected by filtration, and the dry ether extracts were treated with excess ethanolic hydrogen chloride. The solvents were removed *in vacuo* leaving a viscous residue which was dissolved in methanol and dried by repeated evaporation with a benzene-methanol mixture *in vacuo* on the steam bath.

The frothy residue was pulverized and dried *in vacuo* at 45° for 18 hr.; yield, 37.5 g. (60%) of a hygroscopic, pale yellow powder, m.p. indefinite, beginning at 120°.

Anal. Calcd. for $C_{40}H_{62}N_4O_2 \cdot 4HCl$: C, 61.84; H, 8.56; N, 7.21. Found: C, 61.72; H, 8.86; N, 6.99.

6,6′-Diallyl-α,α′-bis[(3-diethylaminopropyl)methylamino]-4,4′-bi-*o*-cresol Tetrahydrochloride (IVd).—To a mixture of 8.0 g. (0.03 mole) of 2,2′-diallyl-*p,p*′-biphenol and 25 ml. of 95% ethanol was added with shaking 8.6 g. (0.06 mole) of N,N-diethyl-N′-methyl-1,3-propanediamine and 4.5 ml. (0.06 mole) of 40% aqueous formaldehyde solution. An exothermic reaction occurred, and the solution turned dark brown in color. After standing for 0.5 hour, the mixture was boiled under reflux for 2 hr. The reaction mixture was dissolved in ether and the solution was washed thoroughly with 5% sodium hydroxide solution and water. The ether solution was dried over anhydrous potassium carbonate and the ether evaporated on a steam bath. The gummy residue was treated with an excess of concentrated hydrochloric acid, benzene was added, and the mixture evaporated to dryness *in vacuo* on the steam bath. Attempted crystallization of the residue from a 2-propanol–acetone mixture yielded a waxy solid, which was collected by filtration, dissolved in water, made alkaline with sodium hydroxide solution and extracted with ether. The combined ether extracts were washed thoroughly with 10% sodium hydroxide solution and water and dried successively over solid potassium hydroxide and anhydrous potassium carbonate. Attempts to prepare crystalline sulfate and salicylate salts failed. The ether solution was treated with decolorizing charcoal and dry hydrogen chloride was bubbled into the ether filtrate. The pale yellow solid was collected by filtration and dried *in vacuo* at room temperature for 20 hr; yield 15 g. (60%), m.p. indefinite, foaming at 100°.

Anal. Calcd. for $C_{36}H_{58}N_4O_2 \cdot 4HCl$: C, 59.66; H, 8.62; N, 7.73. Found: C, 59.70; H, 8.92; N, 7.08.

6,6′-Diallyl-α,α′-bis[bis(2-diethylaminoethyl)amino]-4,4′-bi-*o*-cresol Hexahydrochloride (Va).—A warm solution of 13.5 g. (0.063 mole) of 1,1,7,7-tetraethyldiethylenetriamine and 1.9 g. (0.063 mole) of paraformaldehyde in 100 ml. of 95% ethanol was added to a solution of 8.0 g. (0.03 mole) of 2,2′-diallyl-*p,p*′-biphenol in 100 ml. of 95% ethanol, and the mixture boiled under reflux for 2.5 hr. The ethanol was removed *in vacuo* on the steam bath. The residue was dissolved in ether and the ether solution washed thoroughly with successive portions of water, 10% sodium hydroxide solution, and water. After treatment with excess ethanolic hydrogen chloride, the ether was removed on the steam bath, benzene was added and the mixture evaporated *in vacuo*. The hygroscopic salt was dissolved in water (decolorizing charcoal), made alkaline with ammonium hydroxide, and the base extracted with ether. The ether extracts were washed with water, the ether removed *in vacuo*, and the residue dis-

solved in petroleum ether (b.p. 30–60°). The petroleum ether solution was decanted from insoluble impurities, treated with decolorizing charcoal and filtered. The solvent was removed *in vacuo*, the residue treated with an excess of ethanolic hydrogen chloride and the mixture evaporated to dryness *in vacuo* on the steam bath. The residue was pulverized and dried *in vacuo* at 45° for 18 hr.; yield, 13 g. (46%), m.p. indefinite, foaming at 100°.

Anal. Calcd. for $C_{44}H_{76}N_6O_2 \cdot 6HCl$: C, 56.22; H, 8.79. Found: C, 56.64; H, 8.65.

6,6′-Diallyl-α,α′-bis[bis(3-diethylaminopropyl)amino]-4,4′-bi-o-cresol Hexahydrochloride (Vb).—A mixture of 15.3 g. (0.063 mole) of 3,3′-bis(diethylamino)dipropylamine and 1.9 g. (0.063 mole) of paraformaldehyde in 100 ml. of 95% ethanol was warmed until a clear solution was obtained. The cooled solution was subsequently added to a solution of 8.0 g. (0.03 mole) of 2,2′-diallyl-*p,p′*-biphenol in 100 ml. of 95% ethanol, and the mixture boiled under reflux on the steam bath for 2 hr. The ethanol was allowed to evaporate, the residue was dissolved in ether, and the ether extracts were washed several times with 10% sodium hydroxide solution and water. The ether solution was then extracted thoroughly with *N* acetic acid solution, the acetic acid extracts were made strongly alkaline by the addition of sodium hydroxide, and the base was extracted with ether. The ether solution was treated with excess concd. hydrochloric acid, allowed to stand for several hr., made strongly alkaline with ammonium hydroxide and the base again extracted with ether. The ether extracts were washed with water, treated with decolorizing charcoal, and dried over anhydrous potassium carbonate. The drying agent was collected by filtration, and the ether filtrate treated with anhydrous hydrogen chloride. The sticky mass which separated was dissolved in methanol, treated with ethanolic hydrogen chloride, and the solvent removed *in vacuo* at room temperature. The hygroscopic white powder thus obtained weighed 19.5 g. (64%), m.p. 110°.

Anal. Calcd. for $C_{48}H_{84}N_6O_2 \cdot 6HCl \cdot H_2O$: C, 56.85; H, 9.14; N, 8.28. Found: C, 57.02; H, 8.95; N, 8.15.

Preparation of Amidines by Catalytic Reduction of Amidoximes

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Recently[1] several large-membered heterocyclic compounds possessing side chains with terminal amidoxime or guanidine groups were prepared and found to manifest antihypertensive activity. Similar compounds with respect to the heterocyclic moiety of the molecule, but with an amidine instead of the amidoxime or guanidine group are

(1) R. P. Mull, P. Schmidt, M. R. Dapero, J. Higgins, and M. J. Weisbach, *J. Am. Chem. Soc.*, **80**, 3769 (1958); R. P. Mull, M. E. Egbert, and M. R. Dapero, *J. Org. Chem.*, **25**, 1953 (1960).