dry ether, maintaining the temperature throughout at −10° by a Dry Ice–acetone bath. At the completion of addition the temperature was allowed to rise to 4° and stirred for 30 min. The solution was decanted into a dropping funnel through a glass-wool plug and protected from moisture. It was added dropwise to a stirred solution of 12.5 g. (0.039 mole) of 4-(4′-hydroxy-3′,5′-dimethylphenoxy)-3,5-dimethylphenyl bromide in 30 ml. of dry ether at room temperature. After stirring for 0.5 hr. it was allowed to stand for 2 hr. and then poured onto a large amount of powdered Dry Ice covered with ether in a 1-l. flask. After standing overnight, dilute hydrochloric acid was added and the product extracted with ether. The ether solution was in turn extracted with saturated sodium bicarbonate solution until no more carbon dioxide was liberated. The bicarbonate extract was acidified to give an oil that crystallized and was purified from ethanol-water, m.p. 187.5–190.5° after three recrystallizations. There was obtained 5.0 g. (0.0175 mole, 45%).

Anal. Calcd. for $C_{17}H_{18}O_4$: C, 71.31; H, 6.34. Found: C, 71.09; H, 6.37.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF KENTUCKY]

Potential Curare-Like Compounds Derived from Bisdialkylaminoalkyl Esters of Some 3-Phenylglutaric Acids

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A series of bisquaternary ammonium salts derived from dialkylaminoalkyl esters of substituted 3-phenylglutaric acids has been prepared and tested for curare-like activity and for possible hypotensive activity. The esters were prepared by reaction of basic alcohols with the substituted glutaric anhydride, followed by esterification of the resulting half-esters.

Studies on relatively simple molecules[1-3] have indicated that many compounds exhibit some degree of curare-like activity if they possess two quaternary ammonium groups properly spaced with respect to each other. In some cases the activity of the compound can be correlated with the number of atoms between the two quaternary groups. While the importance of the correctly spaced quaternary groups has been discounted,[4] various experimental results[5] do indicate that the nature of the intervening groups, as well as the distance between quaternary ammonium groups, is of importance in determining the degree of curare-like activity.

In order to learn more about the effects of structural changes in that part of the molecular between the quaternary ammonium groups we have prepared a series of esters in which two quaternary ammonium groups are either eleven or thirteen atoms apart and in which certain variations are made in the nature of the molecule between the two quaternary ammonium groups (Table I). It will be noted that in all of these structures a rather bulky group (phenyl or substituted phenyl) is present in the central part of the molecule. This is in contrast to some of the other synthetic curare-like compounds[1-3] which are essentially linear molecules with no bulky groups in the central part of the molecule. Tubocurarine chloride, by contrast, is a very bulky molecule.

The compounds listed in Table I are of interest both for their value in correlating structure with curare-like activity and also for their possible value as hypotensive agents.

The substituted phenylglutaric acids could not be converted to basic esters by direct esterification in benzene because of the low solubility of the acid in benzene. The satisfactory synthesis of the esters made use of the increased solubility of the anhydrides, compared with the acids, and the faster reaction rate in toluene, compared with benzene. The basic esters prepared in this way were oils, and were converted without purification to the corresponding bisquaternary ammonium salts.

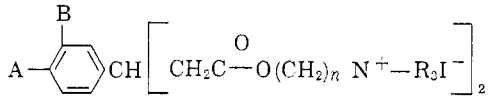
The curare-like activity of compounds in this series (Table II) decreases with substitution on the phenyl ring. This decrease in activity is noted whether the substituent is methoxyl, nitro, or both. The detrimental effect of these substituents appears to be cumulative.

A comparison of compounds 6 and 7 indicates that lengthening the chain between the quaternary ammonium groups from eleven atoms to thirteen atoms increases the activity of the compound. However, no such correlation is found with compounds 8 and 9. These differ only with respect to the distance between quaternary groups, but both have the same activity.

In this series, minor changes in structure can give rise to striking changes in effect on blood pressure. The two compounds which cause an in-

(1) R. B. Barlow and H. R. Ing, *Nature*, 161, 718 (1948)
(2) W. D. M. Paton and E. J. Zaimis, *Nature*, 161, 718 (1948).
(3) A. P. Phillips, *J. Am. Chem. Soc.*, 71, 3264 (1949).
(4) S. Loewe and S. C. Harvey, *Arch. exptl. Path. Pharmakol.*, 214, 214–16 (1952).
(5) A. P. Phillips, *J. Am. Chem. Soc.*, 77, 2400–2 (1955).

TABLE I



No.	A	B	R	M.P.	Yield, %	Formula	Iodine, % Calcd.	Iodine, % Found
1	H	H	CH_3	100	38	$C_{21}H_{36}N_2O_4I_2$	40.0	40.0
2	CH_3O	H	CH_3	188	43	$C_{22}H_{38}N_2O_5I_2$	38.2	38.0
3	H	NO_2	CH_3	182	45	$C_{21}H_{35}N_3O_6I_2$	37.4	37.2
4	NO_2	H	CH_3	194.5	61	$C_{21}H_{35}N_3O_6I_2$	37.4	37.1
5	CH_3O	NO_2	CH_3	160.5	56	$C_{22}H_{37}N_3O_7I_2$	35.8	35.6
6	H	NO_2	C_2H_5	156	71	$C_{27}H_{47}N_3O_6I_2$	33.2	33.1
7[a]	H	NO_2	C_2H_5	137	21	$C_{29}H_{51}N_3O_6I_2$	32.1	32.0
8	NO_2	H	C_2H_5	183.3	64	$C_{27}H_{47}N_3O_6I_2$	33.2	33.1
9[a]	NO_2	H	C_2H_5	96	38	$C_{29}H_{51}N_3O_6I_2$	32.1	31.5
10	CH_3O	NO_2	C_2H_5	155.2	22	$C_{28}H_{49}N_3O_7I_2$	32.0	31.8

[a] $n = 2$ except in compounds 7 and 9, in which cases $n = 3$.

TABLE II

No.	Curare-like Activity: % Reduction in Twitch Height and Dose (Mg./Kg.)		Curare-like Activity: Dose Causing Failure to Maintain Tetanus (Mg./Kg.)	Blood P. Change: %	Blood P. Change: Mg./Kg.
1	75	0.5[a]	0.25	None	
2	50	2	1	−3	16
3	66	2	1	−58	4
4	50	2	1	[b]	
5	50	3	2	[b]	
6	100	2	2	−34	1
7	100	1	1	+15	1
8	100	1	1	None	
9	100	1	1	+22	1
10	100	2	1	−29	1

[a] 100% Reduction at 1 mg./kg. [b] Transient fall after each injection.

crease in blood pressure are the only members of the series with thirteen (rather than eleven) atoms between the quaternary ammonium groups. The data here are too limited to warrant any conclusions as to the effect of spacing of the quaternary groups on the effect on blood pressure, but this will be the subject of future study.

The effect of minor changes in structure on blood pressure is well illustrated by compounds 3 and 4.

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The authors are indebted to the Lilly Research Laboratories, Indianapolis, Indiana, for the results of the biological testing reported here.

EXPERIMENTAL

All melting points were taken on a Fisher-Johns melting point block, and are corrected.

Glutaric acids. 3-*p*-Methoxyphenylglutaric acid, m.p. 164°, and 3-phenylglutaric acid, m.p. 138°, were prepared in 62–66% yields by a previously described procedure[6] except that it was necessary to handle the hot alkaline solutions in such a way as to minimize exposure to the air and thus prevent air oxidation of the products. 3-(*m*-Nitrophenyl)glutaric acid (71%) m.p. 205–206°, and 3-(*p*-nitrophenyl)glutaric acid (59–83%), m.p. 235°, were prepared by the method of Knoevenagle[7,8] except that 10% alkali was used and no heat was applied. The reaction mixtures were simply allowed to stand at room temperature until solution was complete (1.5 hr. for the *m*-isomer, 8 hr. for the *p*-isomer).

3-(p-Methoxy-m-nitrophenyl)glutaric acid. In a 250-ml. three necked flask fitted with a thermometer, stirrer, and dropping funnel was placed a slurry of 15 g. (0.063 mole) of 3-(*p*-methoxyphenyl)glutaric acid in 75 ml. of acetic acid and 50 ml. of acetic anhydride. The flask was cooled by an ice bath to 5°. To the mixture was slowly added 7.8 ml. (0.12 mole) of concd. nitric acid in 25 ml. of acetic acid at such a rate the temperature remained below 5° throughout the addition. The bath was left in place and the mixture was allowed to warm to room temperature overnight. The reaction mixture, which was homogeneous at this point, was poured over chipped ice. The solution was then evaporated on a steam bath. Successive additions of water during the evaporation were used to remove most of the acetic acid. When the volume was reduced to approximately 150 ml. the solution was allowed to cool and the crystalline product was removed by filtration. There was thus obtained 15.5 g. (87%) of the canary yellow acid, m.p. 165.8–168.8°. Neutralization equivalent, calcd., 141.6; found, 143.7. Further identification is based on conversion to the anhydride below.

3-(p-Methoxy-m-nitrophenyl)glutaric anhydride. A mixture of 10 g. (0.035 mole) of 3-(*p*-methoxy-*m*-nitrophenyl)glutaric acid, 100 ml. of toluene, and 10 ml. (0.1 mole) of acetic anhydride was refluxed for 2 hr. On cooling to −10° there was obtained 8.7 g. (94%) of the anhydride, m.p. 163.7–165.2°.

Anal. Calcd. for $C_{12}H_{11}O_6N$: N, 5.28. Found: N, 5.10.

The above procedure was used to prepare 3-phenylglutaric anhydride, m.p. 106–107°,[9] its *m*-nitro derivative, m.p. 171°,[10] its *p*-nitro derivative, m.p. 122°,[11] and its *p*-methoxy derivative, m.p. 157°[12] in 83–95% yields.

(6) W. T. Smith, Jr., and P. Kort, *J. Am. Chem. Soc.*, **72**, 1878 (1950).
(7) E. Knoevenagel, *Ann.*, **303**, 235 (1898).
(8) E. Knoevenagel, *Ann.*, **303**, 239 (1898).
(9) S. Avery and R. Bouton, *Am. Chem. J.*, **20**, 513 (1898).
(10) S. Avery and H. T. Beans, *Am. Chem. J.*, **28**, 57 (1902).
(11) S. Avery and M. C. Gare, *Am. Chem. J.*, **28**, 53 (1902).
(12) J. G. Jackson and J. Kenner, *J. Chem. Soc.*, 1660 (1928).

Bisquaternary ammonium salts. The two following procedures are representative of the methods used in preparing the bisquaternary ammonium salts. The first method was used for compounds 1–5 (Table I) and the second method was used for compounds 6–10.

Bis-2-dimethylaminoethyl 3-(p-nitrophenyl)glutarate bismethiodide. In a 250-ml. flask fitted with a Dean-Starke water trap[13] were placed 150 ml. of dry toluene, 8 g. (0.034 mole) of 3-(*p*-nitrophenyl)glutaric anhydride, and 10 ml. (0.10 mole) of 2-dimethylaminoethanol. This mixture was refluxed for 2 days, by which time no more water was being collected in the trap. The solution was washed with three-30 ml. portions of water and the toluene was evaporated. The resulting oil was taken up in 50 ml. of methanol, and 8 ml. of methyl iodide was carefully added. Reaction occurred readily as evidenced by spontaneous refluxing of the solution. The mixture was refluxed for 1 hr., allowed to stand overnight, and cooled to complete precipitation of the product. Recrystallization from 100 ml. of methanol gave 14.1 g. (61% based on anhydride), m.p. 193.5–194.5°.

Gentle saponification of the water washings followed by acidification resulted in the recovery of 3.3 g. of 3-(*p*-nitrophenyl)glutaric acid. This represents 38% of the starting anhydride.

Bis-2-diethylaminoethyl 3-(m-nitrophenyl)glutarate bisethiodide. Using the same procedure as above, 8 g. (0.034 mole) of 3-(*m*-nitrophenyl)glutaric anhydride and 10 ml. (0.073 mole) of 2-diethylaminoethanol were esterified in toluene. Following the washing and evaporation of toluene, the oil was taken up in 50 ml. of absolute ethanol and treated as above with 6 ml. of ethyl iodide. The product was recrystallized from absolute ethanol to give 18.4 g. (71%), m.p. 154–156°. Saponification of the washings gave 1.3 g. of 3-(*m*-nitrophenyl)glutaric acid, equivalent to 15% of the anhydride used as starting material.

(13) E. W. Dean and D. D. Starke, *Ind. Eng. Chem.*, **12**, 486 (1920)

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF MIAMI]

Synthesis of Potential Anticancer Agents. V. Schiff Bases and Related Compounds[1-2]

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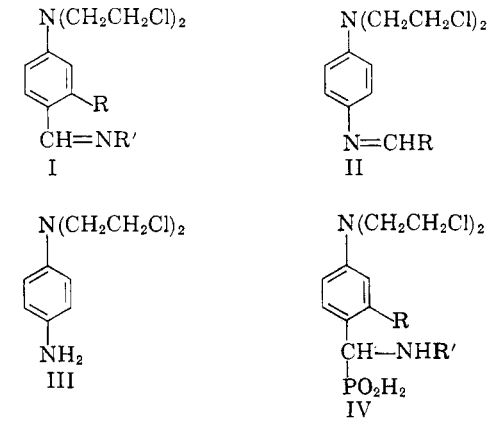
Schiff bases have been prepared by the condensation of amines with benzaldehyde nitrogen mustard and with 4-[bis(2-chloroethyl)amino]-*o*-tolualdehyde; and by the condensation of aldehydes with *N,N*-bis(2-chloroethyl)-*p*-phenylenediamine. Several of these Schiff bases have been converted to aminophosphinic acids.

Some time ago we reported the condensation of benzaldehyde mustard {[*p*-[*N,N*-bis(2-chloroethyl)-amino]benzaldehyde}4-[bis(2-chloroethyl)amino]-*o*-tolualdehyde, *p*-diethylaminobenzaldehyde, and *p*-[*N*-ethyl-*N*-(2-chloroethyl)amino]benzaldehyde with a variety of amines.[4] Although the Schiff bases prepared from the last two aldehydes exhibited little or no activity against the Dunning lukemia in rats, the Schiff bases (I) from the first two aldehydes exhibited, in many cases, wide ranges of activity as well as a few cures.[5] On the basis of the compounds reported earlier[4] little could be derived in the way of structure to activity relations except that, with the same amine, the Schiff bases (I. R = CH_3) from 4-[bis(2-chloroethyl)amino]-*o*-tolualdehyde were



generally more active than the ones from benzaldehyde mustard.

In order to determine if any structure to activity relationships exist and in hopes of finding a more active anticancer agent we have now extended this series to include those Schiff bases listed in Table I. As before[4] the crystalline Schiff bases (I) were obtained by heating the reactants in absolute ethanol.

Although the screening data are not complete, it appears[5] that the Schiff bases from cycloalkylamines are the most active of the anils from aliphatic amines. Further, *N*-[4-bis(2-chloroethyl)amino-2-methylbenzylidene] cyclopentylamine (I. R = CH_3, R' = cyclopentyl) was the most active Schiff

(1) Part IV, F. D. Popp, *J. Org. Chem.*, **26**, 3020 (1961).

(2) This investigation was supported by a Research Grant (T 177) from the American Cancer Society, a Research Grant (CY 4814) from the National Cancer Institute, U. S. Public Health Service, and a grant from an American Cancer Society Institutional Grant to the University of Miami.

(3) Presented in part before the Division of Medicinal Chemistry of the American Chemical Society, St. Louis, Mo., March 1961; and in part at the Caribbean Chemical Symposium at the University College of the West Indies, Jamaica, April 1961.

(4) F. D. Popp, *J. Org. Chem.*, **26**, 1566 (1961).

(5) Drs. Ralph Jones, Jr., and Leo Rane, private communication. Detailed screening results of the compounds mentioned will be reported elsewhere at a later date.