Intestinal Anthelmintics. I. The Preparation of Bis(2,4,5-trichlorophenol)–Piperazine Salt (Triclofenol Piperazine) and Other Phenol–Piperazine Salts

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Although recent progress has been made in the development of new anthelmintics, an efficient, single-dose drug useful for mass treatment of *Ascaris*, hookworms and *Trichuris* is still needed. Piperazine and conventional piperazine salts are used in man to remove *Enterobius* or *Ascaris*, but they have little or no effect against either hookworms or whipworms.[1] Futher, the difficulty usually associated with the formulation and administration of phenolic anthelmintics is well recognized.[2] This report is concerned with a series of new phenol-piperazine salts prepared in the search for a broad-spectrum anthelmintic having pharmaceutically acceptable chemical and physical properties.

The phenol-piperazine salts (Table I) were prepared by the interaction of the appropriate phenol and piperazine in anhydrous benzene. The salts were tested against nematodes in mice by Dr. P. E. Thompson and co-workers of these laboratories.[3] When indicated, expanded testing was carried out against nematodes in rats, cats, dogs and rabbits. The most promising compound studied is bis-(2,4,5-trichlorophenol)-piperazine salt (triclofenol piperazine (CI-416), a salt containing 82.1 per cent. 2,4,5-trichlorophenol and 17.9 per cent. piperazine.[4] The drug is compatible with gelatin capsules and has broad-spectrum activity against intestinal nematodes in experimental animals[5–7] at non-toxic dose levels. In mice, triclofenol piperazine was active against *Nematospiroides dubius*, *Syphacia obvelata* and *Aspiculuris tetraptera* when it was administered in a single dose by gavage. Against *N. dubius*, the compound was two to four times as potent as hexylresorcinol. In rats, *S. muris* was highly susceptible

(1) E. Bueding and C. Swartzwelder, *Pharmacol. Revs.*, **9**, 329 (1957).
(2) H. W. Brown, *Clin. Pharmacol. and Therap.*, **1**, 87 (1960).
(3) For a description of test methods, see H. G. Sheffield, J. E. Meisenhelder and P. E. Thompson, *J. Parasitol.*, **45**, 653 (1959).
(4) F. W. Short and E. F. Elslager, U. S. Patent 2,980,681, April 18, 1961.
(5) P. E. Thompson, D. E. Worley and P. McClay, *J. Parasitol.*, in press.
(6) D. E. Worley, to be published.
(7) A. Pēna Chavarria, K. O. Courtney and P. E. Thompson, Meeting, American Society of Tropical Medicine and Hygiene, Washington, D. C., November 1–4, 1961.

TABLE I

SUBSTITUTED PHENOL–PIPERAZINE SALTS

-Phenol	Yield, %	M.p., °C.[a]	Composition, ·$C_4H_{10}N_2$	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found
2,4,5-Trichloro-	91	109–110	$2C_6H_3Cl_3O$[b]	39.9	40.0, 40.3	3.4	3.8, 3.7	5.8	6.2, 6.1
2,4,6-Trichloro-	25[c]	147–149	$2C_6H_3Cl_3O$					5.8	5.9
2-Bromo-4-chloro-	82	86–88	$2C_6H_4BrClO$					5.6	5.5
Resorcinol	69[d]	187–189	$C_6H_6O_2$	61.2	61.4	8.2	8.1	14.3	13.9, 13.8
4-Chloro-3,5-dimethyl-	90	130–132	$2C_8H_9ClO$	60.2	60.8, 60.5	7.1	7.2, 7.4	7.0	7.0
1-Bromo-2-naphthol	90	93–95	$2C_{10}H_7BrO$	54.2	54.2	4.5	4.9	5.3	5.4
4-*tert*-Butyl-2,6-dichloro-	99	171–172	$2C_{10}H_{12}Cl_2O$					5.3	5.3
4-*tert*-Butyl-2-chloro-	60	114–115	$2C_{10}H_{13}ClO$	63.3	63.7	8.0	8.0	6.2	5.7, 5.7
5-Chlorocarvacrol	90	86.5–88	$2C_{10}H_{13}ClO$					6.2	6.1
6-Chlorothymol	83	117–119	$2C_{10}H_{13}ClO$					6.2	6.1
p-*tert*-Butyl-	81	95–96	$2C_{10}H_{14}O$	74.6	74.8	9.9	10.0	7.3	6.8, 7.0
p-(1,1-Dimethylpropyl)-	60	91–92	$2C_{11}H_{16}O$	75.3	75.5	10.2	10.6	6.8	6.8
4-Bromo-2-phenyl-	90	118–120	$2C_{12}H_9BrO$	57.6	57.9	4.8	5.0	4.8	4.7
o-Phenyl-	89	139–139.5	$2C_{12}H_{10}O$					6.6	6.7
p-Phenyl-	76	155–157	$2C_{12}H_{10}O$					6.6	6.4
p-Phenoxy-	80	119–121	$2C_{12}H_{10}O_2$	73.3	73.8	6.6	6.9	6.1	6.3
2-Bromo-4-cyclohexyl-	88	114–116	$2C_{12}H_{15}BrO$	56.4	57.0	6.8	7.0	4.7	4.6
4-Chloro-2-cyclohexyl-	87	127–128	$2C_{12}H_{15}ClO$	66.3	66.7	7.9	8.1	5.5	5.3, 5.4
m-Cyclohexyl-	70	103–106	$2C_{12}H_{16}O$	76.7	76.7, 76.8	9.7	9.7, 9.8	6.4	6.6, 6.6
2,5-Diisopropyl-	11	97–100	$2C_{12}H_{18}O$					6.3	6.2
2,6-Diisopropyl-	82[e]	64–66	$2C_{12}H_{18}O$	76.0	75.9	10.5	10.5	6.3	6.2
4-Hexylresorcinol	94	98–101	$2C_{12}H_{18}O_2$					5.9	6.0
2,2′-Methylenebis-(4,6-dichlorophenol)	85	214–218	$C_{13}H_8Cl_4O_2$	48.1	48.5	4.3	4.5	6.6	6.3

TABLE I (*Continued*)

-Phenol	Yield, %	M.P.,[a] °C.[a]	Composition, -$C_4H_{10}N_2$	Analyses, % Nitrogen Calcd.	Found
o-Benzyl-	76	70–84	$2C_{13}H_{12}O$	6.2	6.0
p-Benzyl	92	93.5–95	$2C_{13}H_{12}O$	6.6	6.2
4-Chloro-2-(α-methylbenzyl)-	76	85.5–86.5	$2C_{14}H_{13}ClO$	5.1	4.9
p-(α-Methylbenzyl)-	89	86–87	$2C_{14}H_{14}O$	5.8	5.4, 5.3
4-(α,α-Dimethylbenzyl)-pyrocatechol	69	128–130	$C_{15}H_{16}O_2$	8.9	8.7

[a] Melting points are not corrected. [b] Chlorine, calcd., 44.2; found, 43.8, 43.9. [c] After recrystallization from ethanol of a 98% yield of product of m.p. 145–147°. [d] After recrystallization from ethanol of an 89% yield of product of m.p. 186–188°. [e] Recrystallized from low-boiling petroleum ether.

to the drug while *Nippostrongylus muris* was not. In dogs, the trichlorophenol piperazine salt was about as effective as hexylresorcinol against ascarids and hookworms but was more effective than the reference drug against whipworms.[5]

Triclofenol piperazine also exhibits broad-spectrum anthelmintic activity in man. When the compound was administered in single or multiple doses of 30-50 mg./kg., the drug had a strong effect against *Ascaris* and hookworms, a moderate effect against *Enterobius* and *Trichuris*, a slight effect against *Strongyloides*, and it was well-tolerated.[7-9] The drug also removed *Trichostrongylus orientalis* in three patients refractory to treatment with several other anthelmintic.[10] Inasmuch as the average human dose of the compound contains less than one-half as much piperazine as extensive experience has shown is necessary for appreciable effect against either *Ascaris* or *Enterobius*, the drug differs from the conventional piperazine salts both as to the spectrum of activity and the amount of piperazine used.

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Experimental[11]

General Procedure.—The phenols, usually unpurified commercial materials, were dissolved in warm benzene, except resorcinol which was dissolved in ethanol. Anhydrous piperazine in benzene solution was prepared by azeotropic distillation of water from commercial piperazine or piperazine hexahydrate. To 2 moles of the phenol solution was added 1 mole of the piperazine solution, except in the case of resorcinol (1:1), 2,2′-methylenebis-(4,6-dichlorophenol) (1:2), and 4-(*o*,-*α*-dimethylbenzyl)-pyrocatechol (1:1). The 2:1 (phenol:piperazine) salts were obtained, except in the latter three cases where 1:1 salts resulted. The salts were usually obtained crystalline by cooling the reaction solution directly, or after addition of low-boiling petroleum ether. The highly soluble salt from 2,6-diisopropylphenol was obtained by evaporation of the benzene solution. Except where indicated in the table, the salts were characterized and tested without recrystallization. An example will illustrate the general procedure.

(8) E. D. Wagner, *Am. J. Trop. Med. Hyg.*, **10**, 521 (1961).

(9) E. A. Gunders, Annual Rep. Liberian Inst.; Am. Found. Trop. Med., 1960, p. 84.

(10) D. E. Kayhoe, E. Guinn, and G. P. George, Meeting, American Society of Tropical Medicine and Hygiene, Washington, D. C., November 1-4, 1961.

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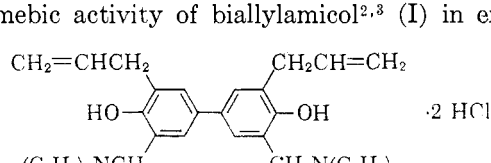
The antiamebic activity of biallylamicol[2,3] (I) in experimental[4,5]



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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.