TABLE III (*continued*)

| Compound | Number or source | NSC no. | S-180 NTL,[b] mg./kg. | S-180 T/C,[c] % | Ca-775 or E.A. NTL, mg./kg. | Ca-775 or E.A. T/C, % | L-1210 NTL, mg./kg. | L-1210 T/C, % |
|---|---|---|---|---|---|---|---|---|
| 5-Chloro-6-methyl | Ref. 1 | 26542 | 500 | 89 | 225 | E 75 | 450 | 78 |
| 5-Bromo-6-methyl | Ref. 1 | 53064 | 300 | 79 | 300 | C 102 | 300 | 84 |
| 5-Chloro-6-ethyl- | IVb | 58562 | 250 | 86 | 62 | C 79 | 125 | 104 |
| 5-Chloro-6-propyl- | IVc | 58563 | 250 | 101 | 125 | C 77 | 250 | 92 |
| 5-Chloro-6-isopropyl- | IVd | 58564 | 125 | 86 | 125 | C 78 | 250 | 87 |
| 5-Chloro-6-heptadecyl- | IVe | 58565 | 250 | 73 | 250 | C 121 | 250 | 95 |
| 5-Chloro-6-phenyl- | IVf | 58567 | 250 | 107 | 250 | C 96 | 250 | 91 |
| Methyl 5-chloroorotate | *e* | 64341 | 500 | 81 | 450 | C 97 | 450 | 104 |
| Part B, Polychloropyrimidines | | | | | | | | |
| 2,4-Dichloro- | Comm. avail. | 37531 | 125 | 87 | 125 | E 112 | 100 | 104 |
| | | | | | 100 | E 147 | | |
| 2,4-Dichloro-6-methyl- | | 13199 | 500 | 71 | 400 | C 100 | 500 | 108 |
| 2,4-Dichloro-6-ethyl- | IIIb | 58568 | 63 | 101 | 125 | C 105 | 63 | 96 |
| 2,4-Dichloro-6-propyl- | IIIc | 58569 | 63 | 75 | 250 | C 108 | 250 | 102 |
| 2,4-Dichloro-6-isopropyl- | IIId | 58570 | 250 | 116 | 62 | C 95 | 62 | 97 |
| 2,4-Dichloro-6-heptadecyl- | IIIe | 58571 | 250 | 93 | 250 | C 87 | 250 | 104 |
| 2,4-Dichloro-6-phenyl- | IIIf | 49018 | 125 | 104 | 25 | C 107 | 100 | 97 |
| 2,4,5-Trichloro- | Va | 40593 | 31 | 86 | 7 | C 124 | 25 | 98 |
| 2,4,5,6-Tetrachloro- | *e* | 35123 | 125 | 49 | 3.75 | C 37 | 1.9 | 104 |
| | | | 30 | 85 | 24 | E 78 | | |
| 6-Methyl-2,4,5-trichloro- | Ref. 1 | 26541 | 500 | 72 | 450 | C 54 | 450 | 111 |
| | | | | | | E *f* | | |
| 6-Bromomethyl-2,4,5-trichloro | Ref. 1 | 30721 | 10 | 47 | 7 | E 131 | 7 | 100 |
| | | | 10 | 70 | | C 85 | | |
| 6-Ethyl-2,4,5-trichloro- | Vb | 58573 | 16 | 95 | 31 | C 91 | 62 | 105 |
| 6-Propyl-2,4,5-trichloro- | Vc | 58574 | 63 | 60 | 31 | C 78 | 62 | 102 |
| 6-Isopropyl-2,4,5-trichloro- | Vd | 58575 | 21 | 68 | 31 | C 117 | 62 | 100 |
| 6-Heptadecyl-2,4,5-trichloro- | Ve | 58576 | 250 | 126 | 250 | C 120 | 250 | 104 |
| 6-Phenyl-2,4,5-trichloro- | Vf | 53184 | 63 | 128 | 15 | C 71 | 250 | 88 |
| 4-Carbomethoxy-2,5,6-trichloro- | Ref. 12 | | 8 | 48 | | | | |
| | | 64342 | 2 | 106 | 2 | C 129 | 2 | 97 |

[a] We are indebted to Dr. Howard Bond, Cancer Chemotherapy, National Service Center, NIH, Bethesda 14, Md., for making these data available to us. The details of the screening procedures can be found in ref. 12. [b] NTL = maximum non-toxic level. [c] T/C = treated tumor/control tumor. [d] C = Carcinoma-755; E = Ehrlich ascites. [e] H. Gershon, *J. Org. Chem.*, **27**, 3507 (1962). [f] Test results on Ehrlich ascites from 3 laboratories:

| Lab | 1 | | | | | | | | | | 2 | | | | 3 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| NTL | 450 | 450 | 450 | 450 | 450 | 450 | 750 | 600 | 450 | 225 | 750 | 600 | 450 | 225 | 225 |
| T/C | 42 | 16 | 20 | 32 | 5 | 34 | 2 | 27 | 0 | 49 | 87 | 78 | 103 | 83 | 116 |

(12) CCNSC Specifications for Screening Chemical Agents and Natural Products Against Animal Tumours, compiled by Drug Evaluations Branch, *Cancer Chemother. Rep.*, **1**, 12 (1959).

acetic acid. About 50–100 mg. of ferric chloride was added, and the solution was brought to near boiling. Sulfuryl chloride (23.0 g., 0.17 mole) was added dropwise with agitation. Upon completion of addition of the sulfuryl chloride, the solution was heated under reflux till no more hydrogen chloride was evolved. The mixture was allowed to cool to room temperature with agitation and 53 g. of product was obtained after filtration and washing with water and acetone. The yield was 89%, m.p. 204–210°. An analytical sample was crystallized from methanol, m.p. 210–211.5°.

**2,4-Dichloro-6-*n*-heptadecylpyrimidine (IIIe).**—A mixture of 35.0 g. (0.1 mole) of IIe in 350 ml. of phosphorus oxychloride was heated under reflux with agitation till hydrogen chloride evolution nearly ceased. The excess phosphorus oxychloride was removed in a flash evaporator and the residue was poured into an ice-water slurry. The dichloropyrimidine was extracted with ether, which was dried, decolorized with charcoal, filtered and evaporated under vacuum. The oily residue did not distil below 190° (0.3 mm.) and could not be purified further.

**6-*n*-Heptadecyl-2,4,5-trichloropyrimidine (Ve).**—A mixture of 29.0 g. (0.075 mole) of IVe in 290 ml. of phosphorus oxychloride was treated as above. A yield of 29.2 g. (92%) of Ve was obtained which could not be distilled below 190° (0.3 mm.) or crystallized.

## Antiamebic Agents. VI.[1] Analogs of Bialamicol and Related Quinolinols

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*Received July 11, 1962*

Bialamicol is a useful antiamebic agent.[4,5] A recent publication[6] in which the diethylamino of bialamicol

(1) Previous paper: J. H. Burckhalter and R. I. Leib, *J. Org. Chem.*, **26**, 4078 (1961).

(2) College of Pharmacy, The University of Michigan, Ann Arbor, Mich.

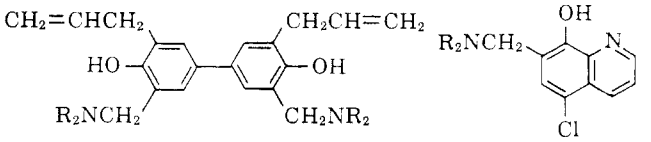
(3) Parke, Davis and Co. Fellow.

(4) J. H. Burckhalter, F. H. Tendick, E. M. Jones, W. F. Holcomb and A. L. Rawlins, *J. Am. Chem. Soc.*, **68**, 1894 (1946). Trade name of bialamicol: Camoform®.

(5) P. E. Thompson, J. W. Reinertson, D. A. McCarthy, A. Bayles and A. R. Cook, *Antibiotics & Chemotherapy*, **8**, 433 (1955); R. V. Taylor, *Am. J. Gastroenterol.*, **26**, 713 (1956).

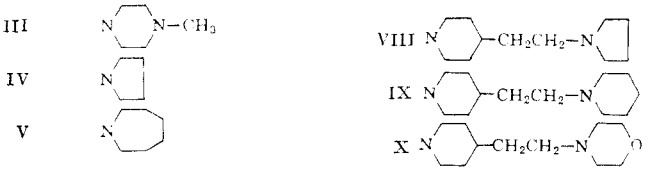
(6) E. F. Elslager and F. H. Tendick, *J. Med. Pharm. Chem.*, **5**, 646 (1962).

(I) "is substituted with basic side chains (*e.g.*, II) similar to those found in antiamebic agents" prompts us to report that, prior to submission of that manuscript,[6] we had already described very promising antiamebic agents with such side chains (*e.g.*, VII).[7] The rationale





| | NR$_2$ | | NR$_2$ |
|---|---|---|---|
| I | N(C$_2$H$_5$)$_2$ | VI | N(C$_2$H$_5$)$_2$ |
| II | NH(CH$_2$)$_3$N(C$_2$H$_5$)$_2$ | VII | NH(CH$_2$)$_3$N(C$_2$H$_5$) |



behind our work was the enhancement of extra-intestinal activity of intestinal amebicides (*e.g.*, VI) through addition of a basic side chain.[7] One of the compounds (VII) now shows promise in the clinic. The recent publication by Elslager and Tendick[6] prompts us to report the syntheses of III and two other analogs of I (IV and V), as well as three analogs of VII (VII, IX and X).

Compounds III, IV and V were synthesized by means of the Mannich reaction from 1,1′-bis-(3-allyl-4-phenol), paraformaldehyde and the appropriate secondary amine. VIII, IX and X originated from the reaction between 5-chloro-8-quinolinol, paraformaldehyde and the appropriate 4-(2-cyclic-aminoethyl)-piperidine.[8] Three corresponding position isomers, 2-(2-cyclic-aminoethyl)-piperidines,[8,10] failed to undergo the Mannich reaction with 5-chloro-8-quinolinol, presumably because of steric hindrance.

Compounds III, IV, V, VIII, IX and X were tested by Dr. P. E. Thompson and co-workers against *Entamoeba histolytica in vitro*.[5] Respective activities expressed in $\gamma$/ml. are 200, 10, 2000, 20, 20 and 20. Compounds III and V were tested as free bases in suspension, which may explain low effectiveness. All others were screened as dihydrochlorides in solution. *In vivo* in rats, III and V were not promising, and IV was active but not sufficiently effective compared with bialamicol to warrant further study. VIII, IX and X were active but unlikely to be superior to 5-chloro-7-(3-diethylaminopropylaminomethyl)-8-quinolinol (KAN-322).[11]

We wish to thank Dr. P. E. Thompson for the pharmacological results.

(7) J. H. Burckhalter, W. S. Brinigar and P. E. Thompson, *Ann. Biochem. and Exptl. Med.* (Calcutta), **20**, 482 (1960); *J. Org. Chem.*, **26**, 4070 (1961); J. H. Burckhalter, V. C. Stephens, H. C. Scarborough, W. S. Brinigar, and W. E. Edgerton, *J. Am. Chem. Soc.*, **76**, 4902 (1954).

(8) Y. S. Chough, M.S. Thesis, University of Kansas, 1957. After these studies had been completed, the substituted piperidines were described in the literature.[9]

(9) A. P. Phillips, *J. Am. Chem. Soc.*, **79**, 2836 (1957).

(10) A. H. Sommers, M. Freifelder, H. W. Wright and A. W. Weston, *ibid.*, **75**, 57 (1953).

(11) J. H. Burckhalter, W. S. Brinigar and P. E. Thompson, *J. Org. Chem.*, **26**, 4070 (1961).

## Experimental

**6,6′-Diallyl-$\alpha,\alpha'$-bis(4-methyl-1-piperazinyl)-4,4′-bi-*o*-cresol (III).**—A mixture of 13.3 g. (0.05 mole) of 1,1′-bis-(3-allyl-4-phenol), 3 g. (0.1 mole) of paraformaldehyde, 10.2 g. (0.1 mole) of N-methylpiperazine and 75 ml. of alcohol was heated at reflux temperature for 2 hr. Removal of most of the solvent left a solid which was crystallized from isopropyl alcohol to give 15.2 g. (60% yield) of III, m.p. 138–142°. Two more recrystallizations elevated the melting point to 145–146°. III is insoluble in water but soluble in mineral acids.

*Anal.* Calcd. for $C_{30}H_{42}N_4O_2$: C, 73.43; H, 8.62. Found: C, 73.41; H, 8.66.

**6,6′-Diallyl-$\alpha,\alpha'$-bis-pyrrolidino-4,4′-bi-*o*-cresol (IV) Dihydrochloride.**—A mixture of 53.2 g. (0.2 mole) of 1,1′-bis-($\beta$-allyl-4-phenol), 13 g. (0.41 mole) of paraformaldehyde, 28.5 g. (0.4 mole) of pyrrolidine and 70 ml. of alcohol was heated on a steam bath for 1 hr. Since some pyrrolidine was lost through the heat of reaction, 8 g. more was added. Heating was continued under an air current until volatile materials were removed and an oily residue remained. An ether–acetone solution was made and an excessive amount of hydrogen chloride gas was led into the solution to precipitate 101 g., a quantitative yield, of crude product, m.p. 204–210°. Recrystallization from isopropyl alcohol gave 72.4 g. (90% yield) of IV dihydrochloride, m.p. 214–215°.

*Anal.* Calcd. for $C_{28}H_{36}N_2O_2 \cdot 2HCl$: C, 66.52; H, 7.58. Found: C, 66.22; H, 7.74.

**6,6′-Diallyl-$\alpha,\alpha'$-bis-(hexamethyleneimino)-4,4′-bi-*o*-cresol (V).**—Hexamethyleneimine[12] was substituted for pyrrolidine in the preceding procedure. Evaporation of volatile solvent gave a solid free base which was recrystallized three times from 2-propanol; yield, 24.3 g. (50%), m.p. 94.2–95.8°.

*Anal.* Calcd. for $C_{32}H_{44}N_2O_2$: C, 78.64; H, 9.08. Found: C, 78.62; H, 9.10.

**5-Chloro-7-[4-(2-pyrrolidino)-ethylpiperidinomethyl]-8-quinolinol (VIII).**—A mixture of 9 g. (0.05 mole) of 4-(2-pyrrolidinoethyl)-piperidine,[8,9] 1.8 g. (0.06 mole) of paraformaldehyde, and 100 ml. of alcohol was heated to boiling. To the mixture 9 g. (0.05 mole) of 5-chloro-8-quinolinol[13] in 150 ml. of alcohol was added over a period of 30 min. After about 8 hr. of heating, a small amount of yellow by-product 7,7′-methylene-bis-(5-chloro-8-quinolinol) was removed by filtration. The filtrate was concentrated by heating on the steam bath under water pump vacuum. A solid residue was recrystallized from alcohol to give 5 g. (27% yield) of VIII, m.p. 135–137°.

*Anal.* Calcd. for $C_{21}H_{28}ClN_3O$: C, 67.45; H, 7.54. Found: C, 67.32; H, 7.51.

**The dihydrochloride** was made by passing dry hydrogen chloride gas into an alcoholic solution of VIII, and recrystallizing from alcohol–water, m.p. 257–258° dec.

*Anal.* Calcd. for $C_{21}H_{28}ClN_3O \cdot 2HCl \cdot 2H_2O$: Cl (ionic), 14.7. Found: Cl, 14.6.

**5-Chloro-7-[4-(2-piperidino)-ethylpiperidinomethyl]-8-quinolinol (IX).**—The procedure of VIII gave 57% yield of IX, m.p. 129.5–130.5°.

*Anal.* Calcd. for $C_{22}H_{30}ClN_3O$: C, 68.10; H, 7.79. Found: C, 68.16; H, 7.86.

**The dihydrochloride** melted at 245–250° dec.

*Anal.* Calcd. for $C_{22}H_{30}ClN_3O \cdot 2HCl \cdot 3H_2O$: Cl (ionic), 13.8. Found: Cl, 13.9.

**5-Chloro-7-[4-(2-morpholino)-ethylpiperidinomethyl]-8-quinolinol (X).**—The procedure of VIII gave 66% of X, m.p. 127–128°.

*Anal.* Calcd. for $C_{21}H_{28}ClN_3O_2$: C, 64.65; H, 7.23. Found: C, 64.53; H, 7.32.

**The dihydrochloride** melted at 260–270° dec.

*Anal.* Calcd. for $C_{21}H_{28}ClN_3O_2 \cdot 2HCl \cdot H_2O$: Cl (ionic), 14.8. Found: Cl, 14.9.

(12) L. Ruzicka, M. Kobelt, O. Häfliger and V. Prelog, *Helv. Chim. Acta*, **32**, 544 (1949).

(13) B. L. Lemke Co., Inc., Lodi, N. J.