Bacteriostats. VII. Substituted Benzylphenols[1]

A. F. McKAY,[2] H. A. BAKER, R. GAUDRY, D. L. GARMAISE, AND R. J. RANZ

L. G. Ryan Research Laboratories of Monsanto Canada Limited, LaSalle, Quebec, and the Research Laboratories of Ayerst, McKenna and Harrison Limited, Montreal, Quebec

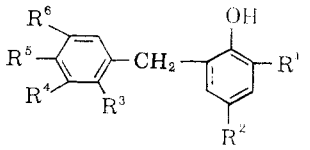
Received May 11, 1965

The effectiveness of the 3,4-dichlorobenzyl group in enhancing the bacteriostatic activities of dithiocarbamate,[3] oxyamines,[4] amidines,[5] and guanidines[1,6] led to the preparation of a series of 2-(3,4-dichlorobenzyl)-phenols for evaluation as bacteriostats. The physical properties of these new benzylphenols are listed in Table I. Most of the compounds were prepared by condensing the appropriate benzyl chloride with the requisite phenol in the presence of catalytic amounts of fused zinc chloride.[7]

Within the experimental variation of the test method the results in Table II indicate that 2-(2,3-dichlorobenzyl)-, 2-(2,4-dichlorobenzyl)-, 2-(2,5-dichlorobenzyl)-, and 2-(3,4-dichlorobenzyl)-4-chlorophenols possess similar antibacterial activities. Thus the 3,4-dichlorobenzyl group does not exhibit any superiority over the other isomeric dichlorobenzyl groups in improving the bacteriostatic activity of 4-chlorophenol. The addition of a second chloro group to the phenol nucleus as in 2-(3,4-dichlorobenzyl)-4,6-dichlorophenol improves the antibacterial activity, but this compound is still not as effective as the commercial product, 2,2'-methylenebis-3,4,6-trichlorophenol (hexachlorophene). 2-Benzyl-4-*n*-butyl-, 2-benzyl-4-*n*-hexyl-, 2-(3,4-dichlorobenzyl)-4-*n*-propyl-, and 2-(3,4-dichlorobenzyl)-4-*n*-butylphenols have the same order of antibacterial activities against Gram-positive bacteria as 2-(3,4-dichlorobenzyl)-4-chlorophenol. The results indicate that the substituents on the phenyl nucleus containing the OH group exert a greater effect on the bacteriostatic activity of the benzylphenols than substituents on the benzyl group. Klarmann, Gates, and Shternov[8] arrived at a similar conclusion from their study of the bactericidal properties of a series of substituted benzylphenols.

TABLE I

SUBSTITUTED BENZYLPHENOLS



No.	R¹	R²	R³	R⁴	R⁵	R⁶	Yield, %	B.p., °C. (mm.)	M.p., °C.	Empirical formula	% C Calcd.	% C Found	% H Calcd.	% H Found	% N Calcd.	% N Found
I	H	C_2H_5	H	H	H	H	44	140–141 (0.35)[a]		$C_{15}H_{16}O$	84.86	84.85	7.60	7.59		
II	H	*n*-C_4H_9	H	H	H	H	36	150–152 (0.25)[b]		$C_{17}H_{20}O$	84.96	85.10	8.39	8.47		
III	H	*n*-C_6H_{13}	H	H	H	H	52	156–162 (0.25)[c]		$C_{19}H_{24}O$	85.01	84.95	9.01	9.30		
IV	H	CH_3	H	Cl	Cl	H	66	168–172 (0.10)	80–81[d]	$C_{14}H_{12}Cl_2O$	62.94	62.66	4.53	4.62	26.54	26.40
V	H	C_2H_5	H	Cl	Cl	H	69	158–161 (0.05)	60.5–61.5[d]	$C_{15}H_{14}Cl_2O$	64.06	64.38	5.01	5.02	25.22	25.21
VI	H	*n*-C_3H_7	H	Cl	Cl	H	68	164–166 (0.15)	64–65[d]	$C_{16}H_{16}Cl_2O$	65.11	65.20	5.46	5.38	21.02	24.34
VII	H	*n*-C_4H_9	H	Cl	Cl	H	65	180–186 (0.5)	59–60[d]	$C_{17}H_{18}Cl_2O$	66.04	65.93	5.87	5.90	22.93	23.07
VIII	H	*n*-C_6H_{13}	H	Cl	Cl	H	71	200–205 (0.5)	44–45[d]	$C_{19}H_{22}Cl_2O$	67.65	67.62	6.58	6.47	21.02	20.85
IX	H	*n*-$C_{18}H_{37}$	H	Cl	Cl	H	74		68–69[d]	$C_{30}H_{50}Cl_2O$	73.64	73.80	9.17	9.17	14.03	14.38
X	H	ClH_2O	H	Cl	Cl	H	63	180–195 (0.2)	102–103[e]	$C_{13}H_{10}Cl_2O_2$	59.39	59.48	4.27	4.50	25.05	25.31
XI	H	C_2H_5O	H	Cl	Cl	H	56	180–184 (0.2)	91–92[d]	$C_{15}H_{14}Cl_2O_2$	60.62	60.47	4.75	4.80	23.86	23.62
XII	H	*n*-C_4H_9O	H	Cl	Cl	H	57	190–198 (0.25)	73–74[e]	$C_{17}H_{18}Cl_2O_2$	62.78	62.57	5.58	5.55	21.80	21.64
XIII[f]	CH_3	3,4-$Cl_2C_6H_3CH_2$					70	150–160 (0.12)	80–81[d]	$C_{14}H_{12}Cl_2O$	62.94	62.96	4.53	4.64	26.51	26.51
XIV	H	Cl	H	NO_2	H	H	67	218–230 (0.1)	114–115[e]	$C_{13}H_9ClNO_4$[f]	59.22	58.98	3.82	3.92	13.45	13.75
XV	H	Cl	Cl	Cl	H	H	69	174–184 (0.1)	58–59[d,g]	$C_{13}H_8Cl_3O$	54.30	54.40	3.16	3.40	36.99	36.76
XVI	H	Cl	Cl	H	Cl	H[h]	80		61–62[d]	$C_{13}H_8Cl_3O$	54.30	54.53	3.16	3.14	36.99	37.29
XVII	H	Cl	Cl	H	H	Cl	71	170–172 (0.1)	56–57[d]	$C_{13}H_8Cl_3O$	54.30	54.14	3.16	3.33	36.99	36.90
XVIII	H	Cl	H	Cl	Cl	H	87	176–180 (0.3)	77–78[d]	$C_{13}H_8Cl_3O$	54.30	54.16	3.16	3.21	36.99	37.31
XIX[h]	Cl	3,4-$Cl_2C_6H_3CH_2$					82	178–180 (0.5)		$C_{14}H_8Cl_4O$	54.30	54.49	3.16	3.35	36.99	36.72
XX	Cl	Cl	H	Cl	Cl	H	50	170–180 (0.2)	91–92[d]	$C_{13}H_8Cl_3O$	48.48	48.55	2.51	2.60	44.04	43.95
XXI	3,4-$Cl_2C_6H_3CH_2$	Cl	H	Cl	Cl	H	10		111–112[e]	$C_{20}H_{12}Cl_6O$	53.79	54.01	2.93	3.01	39.70	39.66

[a] $n^{25}D$ 1.5786, d^{20}_4 0.866. [b] $n^{25}D$ 1.56260, d^{20}_4 0.883. [c] $n^{25}D$ 1.55062, d^{20}_4 1.006. [d] Crystallized from petroleum ether (b.p. 60–90°). [e] Crystallized from ether-petroleum ether (b.p. 60–90°). [f] N, Calcd., 5.31. Found, 5.35. [g] Polymorphic form m.p. 93–94°. [h] Ng. Ph. Buu-Hoi and P. Demerseman, *J. Org. Chem.*, **20**, 1129 (1955), report m.p. 55°. [i] XIII is 2-methyl-4-(3,4-dichlorobenzyl)phenol and XIX is 2-chloro-4-(3,4-dichlorobenzyl)phenol.

Experimental[9]

Chemicals.—4-Methyl-, 4-ethyl-, 4-methoxy-, 4-ethoxy-, 4-*n*-butoxy-, and 4-chlorophenols and 3,4-dichlorobenzyl chloride were purchased from Distillation Products Industries, Rochester, New York. 4-*n*-Butylphenol was obtained from the Aldrich Chemical Company, Milwaukee, Wisconsin. 4-*n*-Octadecylphenol (m.p. 82–83°) was prepared in 84.3% yield from 4-*n*-octadecanoylphenol as previously[10] described.

Substituted Benzylphenols.—The compounds in Table I with the exception of 2,6-di-(3,4-dichlorobenzyl)-4-chlorophenol, 2-

(1) (a) Paper VI: A. F. McKay, D. L. Garmaise, H. A. Baker, L. R. Hawkins, V. Falta, R. Gaudry, and G. Y. Paris, *J. Med. Chem.*, **6**, 587 (1963).

(2) To whom correspondence should be addressed at Monsanto Canada Limited.

(3) A. F. McKay, D. L. Garmaise, R. Gaudry, H. A. Baker, G. Y. Paris, R. W. Kay, G. E. Just, and R. Schwartz, *J. Am. Chem. Soc.*, **81**, 4328 (1959).

(4) A. F. McKay, D. L. Garmaise, G. Y. Paris, and S. Gelblum, *Can. J. Chem.*, **38**, 343 (1960).

(5) D. L. Garmaise, R. W. Kay, R. Gaudry, H. A. Baker, and A. F. McKay, *Ibid.*, **39**, 1493 (1961).

(6) A. F. McKay, *Soap Chem. Specialties*, **36**, 11, 99 (1960).

(7) Ng. Ph. Buu-Hoi and P. Demerseman, *J. Org. Chem.*, **20**, 1129 (1955).

(8) E. Klarmann, L. W. Gates, and V. A. Shternov, *J. Am. Chem. Soc.*, **54**, 3315 (1932).

(9) Microanalyses were performed by Micro-Tech Laboratories, Skokie, Illinois, and Dr. C. Daessle, Montreal, Quebec. Melting points are uncorrected. See paper VI, footnote 4.

(10) A. F. McKay, D. L. Garmaise, G. Y. Paris, S. Gelblum, and R. J. Ranz, *Can. J. Chem.*, **38**, 2042 (1960).

TABLE II

BACTERIOSTATIC ACTIVITIES (m.i.c., $1/X \times 10^{-3}$)[a] OF PHENOLIC DERIVATIVES

No.	*M. pyogenes* var. *aureus* (S)	*M. pyogenes* var. *aureus* (R)	*Sarcina lutea*	*Streptococcus faecalis*	*Escherichia coli* No. 198	*Aerobacter aerogenes*	*Salmonella pullorum*	*Pseudomonas aeruginosa*	*Proteus mirabilis*	*Proteus vulgaris*
I	80	80	80	80	10	10	20	20	20	20
II	1280	1280	1280	640	20	20	20	10	10	10
III	1280	1280	2560	1280	10	20	20	10	10	10
IV	2560	640	640	320	80	10	20	10	40	10
V	640	640	640	640	20	20	20	10	20	10
VI	640	1280	2560	1280	10	<10	<10	<10	<10	<10
VII	2560	2560	5120	2560	20	10	160	20	10	10
VIII	320	320	2560	1280	10	<10		10	10	10
IX	80	80	80	80	20	20	160	10	20	10
X	80	160	320	80	20	10	<10	80	20	10
XI	160	160	320	160	20	10	40	10	20	20
XII	640	640	1280	1280	20	10	20	10	10	10
XIII	640	320	640	320	20	10	10	10	10	10
XIV	160	160	160	160	20	10	10	10	20	20
XV	1280	640	640	640	10	10	80	10	20	20
XVI	1280	1280	1280	1280	80	10	<10	10	40	40
XVII	640	640	1280	320	10	<10	40	10	20	10
XVIII	1280	2560	2560	1280	40	20	20	10	40	40
XIX	640	1280	1280	640	160	20	10	10	10	20
XX	2560	2560	2560	2560	10	10	10	20	20	10
XXI	640	320	160	2560	<10	<10	10	10	10	10
XXII[b]	16000	16000	16000	16000	40	40	40	20	20	20

[a] Minimal inhibitory concentration determined by serial tube dilution technique, *e.g.*, the value of 80 is equivalent to a concentration of one part in 80,000. The serial tube dilution technique can give quite wide variations in results and the relative order of activity is more important than the absolute values listed. [b] Hexachlorophene.

(3,4-dichlorobenzyl)-4,6-dichlorophenol, and 2-(3,4-dichlorobenzyl)-4-*n*-octadecylphenol were obtained by the following procedure which describes the preparation of 2-(3,4-dichlorobenzyl)-4-chlorophenol.

3,4-Dichlorobenzyl chloride (39 g., 0.2 mole) was added over a period of 15 min. to a stirred mixture of 4-chlorophenol (154.3 g., 1.2 moles) and fused zinc chloride (2 g., 0.01 mole) at 100°. This mixture was heated further at 150° for 4 hr. Fractional distillation of the reaction product gave 126.1 g. of unchanged 4-chlorophenol, b.p. 80–100° (0.4 mm.), and 50 g. (87%) of 2-(3,4-dichlorobenzyl)-4-chlorophenol, b.p. 176–180° (0.3 mm.); m.p. 69–74°. Recrystallization from petroleum ether (b.p. 60–90°) raised the melting point to 77–78°.

2,6-Di-(3,4-dichlorobenzyl)-4-chlorophenol.—A mixture of 4-chlorophenol (47.6 g. 0.37 mole), 3,4-dichlorobenzyl chloride (77.1 g., 0.4 mole), and zinc chloride (0.5 g., 0.003 mole) was stirred at 100° for 2 hr. The mixture on distillation gave unchanged reactants, b.p. 60–90° (0.4 mm.); yield 43.5 g. and 36.5 g. (34%) of 2-(3,4-dichlorobenzyl)-4-chlorophenol, b.p. 190–200° (0.3 mm.).

The distillation residue was dissolved in chloroform (200 ml.) and the solution was washed with two 100-ml. portions of water. The chloroform solution was dried over anhydrous sodium sulfate and then evaporated *in vacuo*. The oily residue (30.5 g.) was crystallized from benzene and then from petroleum ether. The purified crystals of 2,6-di-(3,4-dichlorobenzyl)-4-chlorophenol melted at 141–142°, yield 8.6 g. (10.4%).

2-(3,4-Dichlorobenzyl)-4,6-dichlorophenol.—A mixture of 2,4-dichlorophenol (196 g., 1.2 mole) and anhydrous aluminum chloride (5 g.) was stirred at 150° for 1 hr. until hydrogen chloride evolution had ceased. 3,4-Dichlorobenzyl chloride (117 g., 0.6 mole) was added to this stirred mixture at 150° over a period of 30 min. and the heating was continued for an additional 3 hr. The cooled mixture was dissolved in chloroform (500 ml.) and the chloroform solution was washed with 5 *N* hydrochloric acid (500 ml.) and water (500 ml.). This solution was dried over anhydrous sodium sulfate and the chloroform was removed by evaporation. Fractional distillation of the residue gave 100 g. of unchanged 2,4-dichlorophenol, b.p. 60–80° (0.2 mm.), and 135 g. (70%) of 2-(3,4-dichlorobenzyl)-4,6-dichlorophenol, b.p. 170–180° (0.2 mm.); m.p. 80–88°. This product was recrystallized from petroleum ether to a constant melting point of 91–92°, yield 97 g. (50%).

2-(3,4-Dichlorobenzyl)-4-*n*-octadecylphenol.—4-*n*-Octadecylphenol (10.4 g., 0.03 mole) and fused zinc chloride (0.1 g.) were heated to 160° and 3,4-dichlorobenzyl chloride (1.96 g., 0.01 mole) was added dropwise with stirring. The reaction was held at 150–160° for 1 hr. after which the cooled product was dissolved in ether (75 ml.). The ether solution was washed with water (50 ml.) and dried. After the ether was removed by evaporation, the unchanged reactants [b.p. 212–220° (0.3 mm.), yield 6 g.] were recovered by distillation. The distillation residue was dissolved in benzene (100 ml.) and passed through a silica gel column. The column was eluted with benzene in 200-ml. portions. Fractions I, II, and V on evaporation gave oils while fractions III and IV gave the desired product, yield 3.71 g. (74%). The melting point was raised from 56–68° to a constant value of 68–69° by recrystallizing from petroleum ether.

Some 2-Substituted Aminopurines and Purine Analogs[1]

R. M. CRESSWELL, T. STRAUSS, AND GEORGE BOSWORTH BROWN

Division of Nucleoprotein Chemistry, Sloan-Kettering Institute for Cancer Research; Sloan-Kettering Division of Cornell University Medical College, New York, New York

Received July 11, 1963

Cresswell and Strauss[2] have reported the activating effect of a 5-nitroso group on the nucleophilic displacement of the 2-methylmercapto group in pyrimidines (I → II). From the several 2-substituted amino pyrimidines (III, a = 6-OH; b = 6-NH_2) thus obtained,[2] a number of 8-mercaptopurines (IV), *v*-triazolo[*d*]-pyrimidines (V), and purines (VI) have now been prepared. Their properties are given in Table I.

None of these has yet shown significant tumor inhibitory activity.[3] It is of interest that the 6-amino-8-

(1) This investigation was supported in part by funds from the National Cancer Institute, National Institutes of Health, Public Health Service (Grant No. CY-3190-07), and from the Atomic Energy Commission (Contract No. AT(30-1)-910).

(2) R. M. Cresswell and T. Strauss, *J. Org. Chem.*, **28**, 2563 (1963).

(3) In tests carried out in the Division of Experimental Chemotherapy of this Institute.