

TABLE I

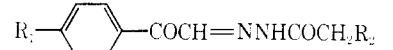
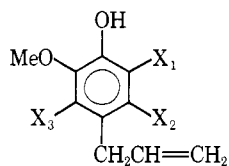
<div style="text-align: center;">  </div>													
No.	R <sub>1</sub>	R <sub>2</sub>	Yield, %	Mp, °C	Solvent of crystn <sup>a</sup>	Formula	C	H	N	Cl	Calcd, %	Found, %	Elemental analysis
1	H	N-Pyrrolidino	40	212-213	E	C <sub>14</sub> H <sub>17</sub> N <sub>3</sub> O <sub>2</sub> ·HCl	56.85	6.13	14.21	11.99		57.09	6.22 14.27 11.83
2	H	N-Piperidino	50	214-215	E-Et	C <sub>16</sub> H <sub>19</sub> N <sub>3</sub> O <sub>2</sub> ·HCl	58.15	6.50	13.56	11.44		58.15	6.65 13.30 11.63
3	H	N-Morpholino	72	138	I	C <sub>14</sub> H <sub>17</sub> N <sub>3</sub> O <sub>3</sub>	61.08	6.22	15.26			61.17	6.15 14.95
4	C <sub>6</sub> H <sub>5</sub>	N-Diethylamino	60	139	E	C <sub>20</sub> H <sub>26</sub> N <sub>3</sub> O <sub>2</sub>	71.19	6.87	12.45			71.12	6.50 12.21
5	C <sub>6</sub> H <sub>5</sub>	N-Pyrrolidino	71	159-160	E-M	C <sub>20</sub> H <sub>21</sub> N <sub>3</sub> O <sub>2</sub>	71.62	6.31	12.53			71.57	6.40 12.83
6	C <sub>6</sub> H <sub>5</sub>	N-Piperidino	71	170-171	E	C <sub>22</sub> H <sub>25</sub> N <sub>3</sub> O <sub>2</sub>	72.18	6.63	12.03			71.97	6.77 11.93
7	C <sub>6</sub> H <sub>5</sub>	N-Morpholino	69	194	M	C <sub>24</sub> H <sub>21</sub> N <sub>3</sub> O <sub>3</sub>	68.36	6.02	11.96			68.64	6.20 11.75
8	C <sub>6</sub> H <sub>5</sub> S	N-Pyrrolidino	68	140	E	C <sub>20</sub> H <sub>21</sub> N <sub>3</sub> O <sub>2</sub> S	65.38	5.76	11.45	8.69 <sup>b</sup>		65.35	6.04 11.58 8.78
9	C <sub>6</sub> H <sub>5</sub> S	N-Piperidino	68	161	E	C <sub>22</sub> H <sub>21</sub> N <sub>3</sub> O <sub>2</sub> S	66.12	6.08	11.03	8.38 <sup>b</sup>		65.99	6.15 10.90 8.37
10	C <sub>6</sub> H <sub>5</sub> S	N-Morpholino	70	144	M	C <sub>24</sub> H <sub>21</sub> N <sub>3</sub> O <sub>3</sub> S	62.65	5.52	10.96	8.36 <sup>b</sup>		62.87	5.49 10.68 8.27
11	C <sub>6</sub> H <sub>5</sub> O	N-Pyrrolidino	65	128	E	C <sub>20</sub> H <sub>21</sub> N <sub>3</sub> O <sub>3</sub>	68.36	6.02	11.96			68.78	6.29 12.30
				189	E	C <sub>20</sub> H <sub>21</sub> N <sub>3</sub> O <sub>3</sub> ·HCl	61.93	5.71	10.83	9.14		61.90	5.62 10.93 9.13
12	C <sub>6</sub> H <sub>5</sub> O	N-Piperidino	45	130	E	C <sub>22</sub> H <sub>23</sub> N <sub>3</sub> O <sub>3</sub>	69.02	6.34	11.50			68.86	6.35 11.73
				170-171	M-Et	C <sub>22</sub> H <sub>23</sub> N <sub>3</sub> O <sub>3</sub> ·HCl	62.75	6.02	10.45	8.82		62.63	6.31 10.55 9.05
13	C <sub>6</sub> H <sub>5</sub> O	N-Morpholino	60	134	E	C <sub>24</sub> H <sub>21</sub> N <sub>3</sub> O <sub>4</sub>	65.38	5.76	11.44			65.35	5.72 11.72
				208-209	E	C <sub>26</sub> H <sub>21</sub> N <sub>3</sub> O <sub>4</sub> ·HCl	59.47	5.16	10.41	8.78		59.72	5.65 10.18 8.83

TABLE I  
 DATA OF BROMO COMPOUNDS OF EUGENOL

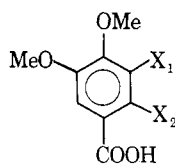
Compd	Bp (mm) or mp, °C	Recrystn solvent	Yield, %	Formula	Calcd, %			Found, %		
					C	H	Br	C	H	Br
II <sup>a</sup>	61	Aq EtOH	71	...	...	...	...	...	...	...
IIa	123-124	EtOH-Me <sub>2</sub> CO	..	C <sub>17</sub> H <sub>14</sub> Br <sub>2</sub> O <sub>3</sub>	47.92	3.31	37.51	47.79	3.36	37.55
III <sup>a</sup>	119-120	Aq EtOH	85	...	...	...	...	...	...	...
IIIa <sup>b</sup>	117	EtOH-Me <sub>2</sub> CO	..	...	...	...	...	...	...	...
VII	186-188 (0.1)	...	73	C <sub>16</sub> H <sub>12</sub> Br <sub>2</sub> O <sub>2</sub>	37.07	3.74	49.33	36.93	3.73	49.17
VIII	165-167 (0.8)	...	32	C <sub>16</sub> H <sub>11</sub> Br <sub>3</sub> O <sub>2</sub>	29.81	2.75	59.53	29.80	2.65	59.36
IX	126-127 (0.3)	...	26	C <sub>16</sub> H <sub>11</sub> BrO <sub>2</sub>	49.40	4.56	32.87	49.53	4.49	32.60
IXa	92	Aq EtOH	..	C <sub>17</sub> H <sub>13</sub> BrO <sub>3</sub>	58.80	4.36	23.02	58.92	4.27	22.84
X	97	Acetic acid	72	C <sub>17</sub> H <sub>13</sub> Br <sub>2</sub> O <sub>3</sub>	40.27	2.98	47.30	40.11	3.16	47.11
XI	149-151 (0.3)	...	54	C <sub>16</sub> H <sub>11</sub> BrO <sub>2</sub>	49.40	4.56	32.87	49.32	4.41	32.73
XIa	68	Aq EtOH	..	C <sub>17</sub> H <sub>13</sub> BrO <sub>3</sub>	58.80	4.36	23.03	58.80	4.39	22.86

<sup>a</sup> See ref 3. <sup>b</sup> E. von Boyen [*Ber.*, **21**, 1393 (1888)] reported mp 113°.

In 1885, Chasanowitz and Hell<sup>3</sup> reported the preparation of a dibromoeugenol and a dibromoeugenol dibromide. The positions occupied by the two nuclear bromine atoms in these compounds were assumed,<sup>4</sup> without sufficient evidence, to be 2 and 5, until Raiford and Perry<sup>5</sup> furnished incontrovertible data to show that these compounds are really 2,3-dibromoeugenol (II) and 2,3-dibromoeugenol dibromide (III), respectively. In 1890, Woy<sup>6</sup> prepared eugenol dibromide benzoate (IV) through bromination of eugenol benzoate (Ia). The preparations of 2,3,5-tribromoeugenol (V) and 2,3,5-tribromoeugenol dibromide (VI) were described by Hell<sup>7</sup> in 1895.



I, X<sub>1</sub> = X<sub>2</sub> = X<sub>3</sub> = H  
 Ia, X<sub>1</sub> = X<sub>2</sub> = X<sub>3</sub> = H; benzoate  
 II, X<sub>1</sub> = X<sub>2</sub> = Br; X<sub>3</sub> = H  
 IIa, X<sub>1</sub> = X<sub>2</sub> = Br; X<sub>3</sub> = H; benzoate  
 V, X<sub>1</sub> = X<sub>2</sub> = X<sub>3</sub> = Br  
 IX, X<sub>1</sub> = Br; X<sub>2</sub> = X<sub>3</sub> = H  
 IXa, X<sub>1</sub> = Br; X<sub>2</sub> = X<sub>3</sub> = H; benzoate  
 XI, X<sub>1</sub> = X<sub>2</sub> = X<sub>3</sub> = H; X<sub>2</sub> = Br  
 XIa, X<sub>1</sub> = X<sub>2</sub> = X<sub>3</sub> = H; X<sub>2</sub> = Br; benzoate  
 III, X<sub>1</sub> = X<sub>2</sub> = Br; X<sub>3</sub> = H  
 IIIa, X<sub>1</sub> = X<sub>2</sub> = Br; X<sub>3</sub> = H; benzoate  
 IV, X<sub>1</sub> = X<sub>2</sub> = X<sub>3</sub> = H; benzoate  
 VI, X<sub>1</sub> = X<sub>2</sub> = X<sub>3</sub> = Br  
 VII, X<sub>1</sub> = X<sub>2</sub> = X<sub>3</sub> = H  
 VIII, X<sub>1</sub> = Br; X<sub>2</sub> = X<sub>3</sub> = H  
 X, X<sub>1</sub> = X<sub>2</sub> = X<sub>3</sub> = H; X<sub>2</sub> = Br; benzoate



XII, X<sub>1</sub> = Br; X<sub>2</sub> = H  
 XIII, X<sub>1</sub> = H; X<sub>2</sub> = Br  
 XIV, X<sub>1</sub> = X<sub>2</sub> = Br

In this paper is described the preparation of the following new bromo compounds of eugenol: eugenol dibromide (VII), 2-bromoeugenol dibromide (VIII), 2-bromoeugenol (IX), 3-bromoeugenol dibromide benzoate (X), 3-bromoeugenol (XI), and 2,3-dibromoeu-

genol benzoate (IIa). Furthermore, new evidence has been provided to confirm the structures of 2,3-dibromoeugenol (II) and 2,3-dibromoeugenol dibromide (III).

**Bromination of eugenol** was conducted with 1, 2, and 3 moles and excess bromine/mole of eugenol. With equimolar proportions of bromine, 2-bromoeugenol dibromide (VIII) was obtained. The position of the nuclear bromine atom was fixed by converting the reaction product to 5-bromoveratric acid (XII), through side-chain debromination, methylation of the phenolic OH group, and oxidation of the allyl side chain. On debromination with zinc and alcohol, 2-bromoeugenol dibromide (VIII) produced 2-bromoeugenol (IX). When 2 moles of bromine was used for bromination, the reaction product could neither be induced to solidify nor be distilled *in vacuo* without decomposition. With 3 moles and more of bromine, 2,3-dibromoeugenol dibromide (III) was obtained.

**Bromination of eugenol benzoate (Ia)** with 1 mole of bromine yielded the reported eugenol dibromide benzoate (IV). On hydrolysis of the benzoate (IV) with 65% H<sub>2</sub>SO<sub>4</sub>, eugenol dibromide (VII) was formed. With 2 moles and more of bromine, eugenol benzoate formed 3-bromoeugenol dibromide benzoate (X). The position of the nuclear bromine atom was determined by converting X to 6-bromoveratric acid (XIII). The corresponding phenol could not be obtained, as the product of hydrolysis decomposed when distilled *in vacuo*. When the crude hydrolyzed product, however, was debrominated with zinc and alcohol and then distilled, an oil was obtained which was found to be 3-bromoeugenol (XI). This compound is particularly interesting in view of the observation that in the one known example of a phenol containing a halogen atom *meta* to the hydroxyl group, 3-halophenol, the bactericidal value is much higher than for the other isomers.<sup>8</sup>

**Bromination of 3-Bromoeugenol Dibromide.**—When crude 3-bromoeugenol dibromide benzoate (X) was debenzoylated and then brominated, there was obtained 2,3-dibromoeugenol dibromide (III). Debromination of III using zinc and alcohol gave 2,3-dibromoeugenol (II). Structural proof of these compounds was obtained by conversion of III to 5,6-dibromoveratric acid (XIV). The above reactions provide additional evidence in support of Raiford and Perry's work<sup>5</sup> on the structures of 2,3-dibromoeugenol dibromide and 2,3-dibromoeugenol. A Schotten-Bau-

(3) L. Chasanowitz and C. Hell, *Ber.*, **18**, 823 (1885).

(4) (a) Th. Zincke and O. Hahn, *Ann.*, **329**, 4 (1903); (b) F. K. Beilstein, "Handbuch der Organischen Chemie," Vol. VI, J. Springer, Berlin, 1923, p 923; (c) I. Heilbron and H. M. Bunbury, "Dictionary of Organic Compounds," Vol. II, Eyre and Spottiswoode, London, 1953, p 86.

(5) L. C. Raiford and R. P. Perry, *J. Org. Chem.*, **7**, 354 (1942).

(6) E. F. R. Woy, *Ber.*, **23** Ref., 204 (1890).

(7) C. Hell, *ibid.*, **28**, 2083 (1895).

(8) M. Klarman, *J. Bacteriol.*, **17**, 440 (1929).

TABLE II  
 ANTIMICROBIAL ACTIVITY<sup>a</sup> OF BROMO COMPOUNDS OF EUGENOL

Compd tested	pH	Antibacterial										Anti-tuberculous		Antifungal		Helminthosporium sativum
		<i>Micrococcus pyogenes</i> var <i>aureus</i>	<i>Bacillus subtilis</i>	<i>Escherichia coli</i>	<i>Salmonella typhosa</i>	<i>Vibrio cholerae</i>	<i>Shigella dysenteriae</i>	<i>Diplococcus pneumoniae</i>	<i>Streptococcus pyogenes</i>	<i>Corynebacterium diphtheriae</i>	<i>Mycobacterium phlei</i>	<i>Mycobacterium 607</i>	<i>Microrosporum gypseum</i>	<i>Trichophyton mentagrophytes</i>	<i>Candida albicans</i>	
I	4.9	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++
	7.0	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++
IX	5.2	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++
	7.0	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++
XI	5.5	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++
	7.0	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++
II	5.5	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++
	7.0	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++
VII	4.9	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
	7.0	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
VIII	4.0	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++
	7.0	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++
III	5.8	+	+	—	—	±	—	+	+	+	+	+	+	+	—	+
	7.0	±	+	—	—	—	—	—	+	+	+	+	+	++	—	+
Ia	5.5	—	—	—	—	—	—	—	—	—	—	—	—	±	—	—
	7.0	—	—	—	—	—	—	—	—	—	—	—	±	±	—	—
IIa	5.5	±	±	±	±	+	±	—	—	—	—	+	±	±	—	—
	7.0	±	±	±	±	±	±	—	—	—	—	±	±	±	—	—
IV	5.5	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
	7.0	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
X	5.5	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
	7.0	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
IIIa	5.8	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
	7.0	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—

<sup>a</sup> The concentration of the compound in the ditch was 10%. The tests for each compound were conducted at the normal pH of the compound and also at pH 7 by using a buffered solution. The activity is shown by: —, confluent growth across the ditch, *i.e.*, no inhibition; ±, sparse growth across the ditch, *i.e.*, slight inhibition; +, growth up to either side of the ditch, *i.e.*, moderate inhibition; ++, absence of growth across the ditch and ending some distance beyond the ditch on either side, *i.e.*, marked inhibition.

mann benzoylation of 2,3-dibromoeugenol (II) produced the corresponding benzoate (IIa) and bromination of the benzoate yielded 2,3-dibromoeugenol dibromide benzoate (IIIa).

Table I summarizes data of these compounds. The bromo compounds of eugenol were tested against a wide range of microorganisms by the ditch-plate technique<sup>9</sup> and have shown marked and, in some cases, specific activity. Results of these tests are summarized in Table II.

#### Experimental Section<sup>10</sup>

**Bromination. General Method.**—A solution of the requisite amount of bromine in 100 ml of acetic acid was added dropwise to a well-stirred, cooled solution of 0.1 mole of the compound to be brominated in 100 ml of acetic acid. The reaction mixture was allowed to stand for 1 hr after the addition of bromine was completed. If any solid product separated, it was filtered and recrystallized. The filtrate was diluted with water, filtered if necessary, and extracted with three 100-ml portions of ether. The ether extract was washed with water and dried (Na<sub>2</sub>SO<sub>4</sub>). The ether was evaporated and the residual oil was distilled *in vacuo*.

**Side-Chain Debromination. General Method.**—A solution of 5 g of the dibromide in 100 ml of ethanol was heated with 10 g of granulated zinc at 70–80° for 2 hr. The reaction mixture was then filtered, the filtrate was diluted with water, and the oil that separated was extracted with three 100-ml portions of ether. The ether extract was dried (Na<sub>2</sub>SO<sub>4</sub>). The ether was evaporated to give a residual oil which was distilled *in vacuo*.

**Hydrolysis of Eugenol Dibromide Benzoates. General Method.**—To a solution of 0.01 mole of the dibromide benzoate in acetic acid was added 3 ml of 65% H<sub>2</sub>SO<sub>4</sub>. Sufficient acetic acid was added to redissolve any solid that was precipitated on addition of the H<sub>2</sub>SO<sub>4</sub>. The mixture was refluxed gently on a steam bath until a test portion showed that the benzoate was completely hydrolyzed. After cooling and diluting with water, the reaction mixture was extracted with ether. The ether was

evaporated and the residual liquid was digested repeatedly with hot water to remove all the benzoic acid. The oil was again taken up in ether. After drying the extract (MgSO<sub>4</sub>), the ether was evaporated and the residual oil was distilled *in vacuo*.

**Conversion of Bromoeugenols to Bromoveratric Acids. General Method.**—The phenol (2.0 ml) from which the side-chain bromine atoms had been removed was dissolved in 20% NaOH solution. To this solution, sufficiently cooled, was added dropwise 5 ml of dimethyl sulfate. The reaction mixture was then refluxed for 0.5 hr. After cooling and diluting with water, it was extracted with ether. The ether extract was washed with dilute H<sub>2</sub>SO<sub>4</sub> and then with water until the washings were neutral to litmus. The ether was evaporated and the residual oil was refluxed for 1 hr with alkaline KMnO<sub>4</sub>. The reaction mixture was acidified (H<sub>2</sub>SO<sub>4</sub>) and excess KMnO<sub>4</sub> was reduced with sodium bisulfite. The solid obtained was filtered and recrystallized from aqueous ethanol or from ligroin (bp 100–120°).

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#### Arylazo Derivatives of Pyridoxine

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Pyridoxine couples readily at pH 8 with aryldiazonium chlorides to give good yields of 6-substituted derivatives (I, Table I). The coupling of pyridoxine with diazonium salts has been recorded as a color

(9) A. Fleming, *Brit. J. Exptl. Pathol.*, **10**, 226 (1929).

(10) Melting points were observed in capillary tubes and are corrected.