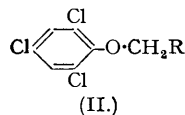
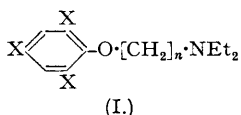


### 564. Antituberculous Compounds. Part I. Halogenated $\omega$ -Aryloxyalkylamines and Analogues.

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A series of chlorinated diethyl-2-phenoxyethylamines has been prepared in an attempt to relate the number and position of the chlorine atoms to the activity against *M. tuberculosis*. The homologation of the diethylaminoalkoxy-group, the replacement of the terminal diethylamino-group by other basic groups, and the replacement of the phenyl nucleus by other aromatic nuclei have also been studied. Although high activities were obtained *in vitro* in certain cases, *in vivo* activity could not be demonstrated.

THE observation by Saz and Bernheim (*J. Bact.*, 1942, **43**, 31) that diethyl-2-(2 : 4 : 6-tri-iodo-phenoxy)ethylamine (I; X = I;  $n = 2$ ) is active *in vitro* against *M. tuberculosis*, and later indications of possible activity *in vivo* (Saz, Johnston, Burger, and Bernheim, *Amer. Rev. Tuberc.*, 1943, **48**, 40; see also Burger, *J. Amer. Pharm. Assoc.*, 1947, **36**, 372), prompted us to examine this substance. The *in vitro* activity, although high, was considerably reduced by the presence of serum in the medium and failure to observe any favourable effect on the course of experimental tuberculosis in guinea-pigs was therefore not unexpected.



This paper describes the preparation of a series of analogues of (I) in an attempt to elucidate the structural features of activity and in the hope of obtaining compounds less prone to deactivation by serum. Following the observation of Burger, Wilson, Brindley, and Bernheim (*J. Amer. Chem. Soc.*, 1945, **67**, 1416) that on a weight basis chloro-derivatives are as effective as iodo-derivatives, a finding which we confirmed in the case of diethyl-2-(2 : 4 : 6-trichloro-phenoxy)ethylamine (I; X = Cl;  $n = 2$ ), work was confined to the more accessible chloro-compounds. The effect of the following structural features was investigated: (1) the extent and position of chlorine substitution; (2) increase of the chain length between the oxygen and nitrogen atoms; (3) replacement of the terminal basic groups by other basic groups; and (4) replacement of the phenyl by naphthyl and quinolyl nuclei, both chlorinated and unchlorinated. Data concerning the compounds prepared are summarised in the table, together with their *in vitro* activities. Detailed biological results will be published elsewhere.

It would appear that in the phenoxy-compounds chlorine, optimally three atoms, is required for the development of maximum activity in the absence of serum, but the activity increment produced by this substitution in most cases disappears in the presence of serum and is therefore unlikely to be reflected in an increased *in vivo* activity. The same effect is observed with diethyl-2-(2 : 4-dichloro-1-naphthoxy)ethylamine. In other cases chlorine has either little effect or even a deactivating effect, *e.g.*, in the case of diethyl-2-(1 : 3-dichloro-2-naphthoxy)ethylamine. Other examples of this effect will be described in a subsequent communication. Although no regularity can be traced between activity and the position of the chlorine atoms, the activities of the isomeric diethyl-2-(trichlorophenoxy)ethylamines differ considerably. The 2 : 3 : 5- and the 2 : 3 : 4-isomers are exceptional in maintaining their high activities in presence of serum. In spite of this, no beneficial effects could be demonstrated with the former on experimental tuberculosis in guinea-pigs. In view of this result and the diminished activity of the pentachloro-derivative, tetrachloro-derivatives were not examined.

The homologous series of compounds (I; X = Cl;  $n = 2, 3, 4, 5$ , or 8) shows an interesting variation of activity. Following a drop of activity when  $n = 3$ , the activity rises to five times the initial activity when  $n = 5$ . With  $n = 8$  the activity has again dropped to the initial value. Deactivation by serum precludes any chemotherapeutic interest in these homologues.

Quaternisation of the terminal diethylamino-group as in *methyldiethyl-2-(2 : 4 : 6-trichloro-phenoxy)ethylammonium chloride* (II; R =  $-\text{CH}_2\cdot\text{NMeEt}_2\text{Cl}$ ), or replacement by an amidino-group as in 2 : 4 : 6-trichlorophenoxyacetamide (II; R =  $-\text{C}(\text{NH})\cdot\text{NH}_2$ ) or by a dihydroglyoxaline group as in 2-(2 : 4 : 6-trichlorophenoxyethyl)-4 : 5-dihydroglyoxaline (II; R =  $-\text{C}\cdot\text{N}\cdot\text{CH}_2\cdot\text{CH}_2\cdot\text{NH}$ ), gives compounds of low activity. Replacement by a di-*n*-octylamino-group [II; R =  $-\text{CH}_2\cdot\text{N}(\text{C}_8\text{H}_{17})_2$ ] also reduces the activity, as in the case of the dibutylamino-group (Burger, *et al.*, *loc. cit.*). A certain specificity therefore attaches to the terminal diethylamino-group or, at least, to a lower dialkylamino-group in this position.

Compound.	Yield.		Base.		Hydrochloride.			Activity.†	
	Method.	%.	B. p.	M. p.	Formula.	Found, N, %.	Reqd., N, %.	In absence of serum.	In presence of serum.
(1) Diethyl-2-phenoxyethylamine .....	A	77	102—104°/4 mm.	136—137°	C <sub>12</sub> H <sub>20</sub> ONCl	6.4	6.1	10	10
(2) Diethyl-2-( <i>p</i> -chlorophenoxy)ethylamine .....	A	77	118—120°/2 mm.	123—124	C <sub>12</sub> H <sub>19</sub> ONCl <sub>2</sub> †	5.4	5.3	10—50	10
(3) Diethyl-2-(2:4-dichlorophenoxy)ethylamine .....	A	71	126—130°/1.5 mm.	131—132	C <sub>12</sub> H <sub>18</sub> ONCl <sub>3</sub> †	4.8	4.7	10	10
(4) Diethyl-2-(2:4:6-trichlorophenoxy)ethylamine .....	B	43	120—124°/1 mm.	163	C <sub>12</sub> H <sub>17</sub> ONCl <sub>4</sub>	4.55	4.2	100	10
(5) Diethyl-2-(2:4:6-tri-iodophenoxy)ethylamine .....	B	50	—	196—198 *	C <sub>12</sub> H <sub>17</sub> ONCl <sub>3</sub>	2.4	2.3	100	10
(6) Diethyl-2-(2:4:5-trichlorophenoxy)ethylamine .....	A	95	117—125°/0.2 mm.	182—183	C <sub>12</sub> H <sub>17</sub> ONCl <sub>4</sub>	4.1	4.2	10 (50)	10 (1000)
(7) Diethyl-2-(3:4:5-trichlorophenoxy)ethylamine .....	A	73	142°/2 mm.	173—174	C <sub>12</sub> H <sub>17</sub> ONCl <sub>4</sub> †	4.4	4.2	10 (100)	—
(8) Diethyl-2-(2:3:5-trichlorophenoxy)ethylamine .....	A	78	135—140°/1 mm.	188—189	C <sub>12</sub> H <sub>17</sub> ONCl <sub>4</sub> †	4.2	4.2	100	50—100
(9) Diethyl-2-(2:3:4-trichlorophenoxy)ethylamine .....	A	89	135°/1 mm.	160—161	C <sub>12</sub> H <sub>17</sub> ONCl <sub>4</sub> †	4.2	4.2	100	100
(10) Diethyl-2-(2:3:6-trichlorophenoxy)ethylamine .....	A	77	135—140°/1 mm.	131.5—132	C <sub>12</sub> H <sub>17</sub> ONCl <sub>4</sub> †	4.4	4.2	50 (100)	10 (500)
(11) Diethyl-2-(pentachlorophenoxy)ethylamine .....	D	—	—	186—187	C <sub>12</sub> H <sub>15</sub> ONCl <sub>6</sub> †	3.5	3.5	1 (100)	5—10
(12) Diethyl-3-(2:4:6-trichlorophenoxy)propylamine .....	A	46	127—135°/1 mm.	162—164	C <sub>13</sub> H <sub>19</sub> ONCl <sub>4</sub> †	4.1	4.0	10	—
(13) Diethyl-4-(2:4:6-trichlorophenoxy)butylamine .....	E	—	—	136—138	C <sub>14</sub> H <sub>21</sub> ONCl <sub>4</sub> †	4.05	3.9	100	—
(14) Diethyl-5-(2:4:6-trichlorophenoxy)- <i>n</i> -amylamine .....	E	—	—	132—133	C <sub>15</sub> H <sub>23</sub> ONCl <sub>4</sub> †	3.8	3.7	500	5 (100)
(15) Diethyl-8-(2:4:6-trichlorophenoxy)octylamine .....	E	—	—	—	—	—	—	100	10
(16) Methyl-diethyl-2-(2:4:6-trichlorophenoxy)ethylammonium chloride .....	—	—	—	235 *	C <sub>9</sub> H <sub>6</sub> ON <sub>2</sub> Cl <sub>4</sub> †	9.6	9.65	5	—
(17) 2:4:6-Trichlorophenoxyacetamide .....	—	—	—	159	C <sub>10</sub> H <sub>10</sub> ON <sub>2</sub> Cl <sub>4</sub> †	8.8	8.9	(1)	—
(18) 2-(2:4:6-Trichlorophenoxyethyl)-4:5-dihydroxyxaline .....	A	60	194—198°/0.2 mm.	175—180	—	—	—	5 (50)	—
(19) Di- <i>n</i> -octyl-2-(2:4:6-trichlorophenoxy)ethylamine .....	C	49	164—166°/2.5 mm.	—	—	—	—	10	—
(20) Diethyl-2-(8-quinolyl)ethylamine .....	C	49	164—166°/2.5 mm.	175—180	—	—	—	1	—
(21) Diethyl-2-(5:7-dichloro-8-quinolyl)oxyethylamine .....	C	45	171°/1 mm.	—	—	—	—	100	10—50
(22) Diethyl-2-(2-quinolyl)ethylamine .....	F	40	131°/0.6 mm.	—	—	—	—	1 (100)	1 (10)
(23) Diethyl-2-( <i>x</i> : <i>x</i> : <i>x</i> -trichloro-2-quinolyl)oxyethylamine .....	F	35	189—191°/1 mm.	195—196	C <sub>15</sub> H <sub>18</sub> ON <sub>2</sub> Cl <sub>4</sub> †	7.2	7.3	100	10
(24) Diethyl-2-(1-naphthoxy)ethylamine .....	C	78	157—160°/2 mm.	159—160	C <sub>18</sub> H <sub>22</sub> ONCl †	5.2	5.0	10—50	10—50
(25) Diethyl-2-(2:4-dichloro-1-naphthoxy)ethylamine .....	C	77	165—166°/0.8 mm.	172	C <sub>16</sub> H <sub>20</sub> ONCl <sub>3</sub> †	4.1	4.0	500	10 (100)
(26) Diethyl-2-(2-naphthoxy)ethylamine .....	C	60	171°/3 mm.	138	C <sub>16</sub> H <sub>22</sub> ONCl †	5.1	5.0	50—100	5—10
(27) Diethyl-2-(1:3-dichloro-2-naphthoxy)ethylamine .....	C	68	173—174°/1 mm.	168	C <sub>16</sub> H <sub>20</sub> ONCl <sub>3</sub> †	4.0	4.0	10	10

\* With decomposition.

† New compound.

‡ Dilution (in thousands) at which complete inhibition of the growth of *M. tuberculosis* (human virulent strain) was maintained for 4 weeks in modified Long's medium (by the floating pellicle method). Figures in parentheses represent dilutions at which partial inhibition occurred. Under the same conditions of test 4-aminosalicylic acid gave a value of 10 in the absence of serum.

For other notes see p. 2682.

Notes to Table (p. 2681).

(1) Burger *et al.* (*loc. cit.*) record m. p. 137·5° for the hydrochloride. (4) Burger *et al.* (*loc. cit.*) record m. p. 160—162° for the hydrochloride. (5) Isolated by extraction of the base from ethereal solution with sulphuric acid, precipitation as the insoluble hydrochloride by addition of excess of hydrochloric acid and recrystallisation from methanol. Long and Burger (*J. Amer. Chem. Soc.*, 1941, **63**, 1586) record m. p. 195—196° (decomp.). For test the hydrochloride was converted into the freely soluble sulphate with one equivalent of silver sulphate. (6) Burger *et al.* (*loc. cit.*) record m. p. 183° for the hydrochloride. (11) The *picrate*, prisms from ethanol, had m. p. 185—186° (Found: N, 9·4.  $C_{18}H_{17}O_8N_4Cl_5$  requires N, 9·4%). (13) 4-(2 : 4 : 6-Trichlorophenoxy)butyl bromide had b. p. 151—154°/5 mm. (14) 5-(2 : 4 : 6-Trichlorophenoxy)-*n*-amyl bromide had b. p. 182—187°/7 mm. The base gave a *picrate*, needles (from ethanol), m. p. 78—80° (Found: N, 9·8.  $C_{21}H_{25}O_8N_4Cl_3$  requires N, 9·9%). (15) Found, for the free base: N, 3·8.  $C_{18}H_{23}ONCl_3$  requires N, 3·7%. (16) The *iodide*, prepared by condensation of compound (4) with methyl iodide in ether, had m. p. 122° (Found: N, 3·3.  $C_{13}H_{19}ONCl_3I$  requires N, 3·2%). The hygroscopic chloride, obtained by treating a methanol solution of the iodide with silver chloride, had m. p. 83—84° (Found: N, 4·0.  $C_{13}H_{19}ONCl_3$  requires N, 4·0%). (19) Preparation by Dr. T. I. Watkins. Found, for the free base: N, 3·0, 3·2.  $C_{24}H_{40}ONCl_3$  requires N, 3·0%. The *Reineckate*, plates (from aqueous acetone), had m. p. 87—88° (Found: N, 11·5; loss at 100°/vac., 4·4.  $C_{28}H_{44}ON_7Cl_3S_4Cr_2H_2O$  requires N, 11·8;  $H_2O$ , 4·4%). (20) Found, for the free base: N, 11·4.  $C_{15}H_{20}ON_2$  requires N, 11·5%. The *dipicrate*, golden yellow rhombohedra from acetone-ethanol, had m. p. 171—171·5° (Found: N, 16·0.  $C_{27}H_{26}O_{15}N_8$  requires N, 15·95%). The hydrochloride was very hygroscopic and not readily purified. (21) The *picrate*, yellow needles from aqueous acetone, had m. p. 154—155° (Found: C, 46·4; H, 3·85; N, 12·7.  $C_{21}H_{21}O_8N_5Cl_2$  requires C, 46·5; H, 3·9; N, 12·9%). (22) Found, for the free base: N, 11·3.  $C_{16}H_{20}ON_2$  requires N, 11·5%. The *picrate*, yellow needles from ethanol, had m. p. 136—137° (Found: N, 14·8.  $C_{21}H_{23}O_8N_5$  requires N, 14·8%). (23) Found, for the free base: N, 8·1.  $C_{15}H_{17}ON_2Cl_3$  requires N, 8·1%. The *picrate*, from dioxan-ethanol, had m. p. 185° (Found: N, 12·1.  $C_{21}H_{20}O_8N_5Cl_3$  requires N, 12·15%). (24) Bovet and Staub, *Compt. rend. Soc. Biol.*, 1937, **124**, 548, mention this substance without chemical details. (25) The *picrate*, needles from aqueous dioxan, had m. p. 177—178° (Found: N, 10·4.  $C_{22}H_{22}O_8N_5Cl_2$  requires N, 10·35%). (26) Einhorn and Rothlauf (*Annalen*, 1911, **382**, 257) record b. p. 202°/18 mm. for the base, and m. p. 138—139° for the hydrochloride.

#### EXPERIMENTAL.

The halogenated phenols were prepared by the following methods: 2 : 4 : 5-trichlorophenol (Harrison, *et al.*, *J.*, 1943, 235); 3 : 4 : 5-trichlorophenol (Kohn and Kramer, *Monatsh.*, 1928, **49**, 161); 2 : 3 : 5-trichlorophenol (Tiessens, *Rec. Trav. chim.*, 1931, **50**, 114); 2 : 3 : 4-trichlorophenol (Hodgson, *J.*, 1930, 1419); 2 : 3 : 6-trichlorophenol (Kohn and Fink, *Monatsh.*, 1930, **56**, 137); pentachlorophenol (Barral and Jambon, *Bull. Soc. chim.*, 1900, [3], **23**, 824); 5 : 7-dichloro-8-hydroxyquinoline (Hebebrand, *Ber.*, 1888, **21**, 2980); 2 : 4-dichloro-1-naphthol (Zincke, *Ber.*, 1888, **21**, 1035); 1 : 3-dichloro-2-naphthol (Zincke, *Ber.*, 1888, **21**, 3386).

**2-Di-*n*-octylaminoethyl Chloride.**—Di-*n*-octylamine (40 g.) and ethylene chlorohydrin (10 c.c. of 60% aqueous solution) were stirred at 100° for 24 hours. The resulting homogeneous solution was cooled and decomposed with 10% sodium hydroxide solution (30 c.c.). The resulting oil, isolated with ether, gave on fractional distillation unchanged di-*n*-octylamine (29 g.) and 2-di-*n*-octylaminoethanol (10 g.) as a colourless oil, b. p. 136—139°/0·2 mm. (Found: N, 5·1.  $C_{18}H_{39}ON$  requires N, 4·9%). The latter (9·1 g.) in chloroform was slowly added to thionyl chloride (5 g.) in chloroform at 0°. After being kept overnight the solution was heated under reflux for 1 hour, and the chloroform evaporated. Crystallisation of the residue from ether afforded 2-di-*n*-octylaminoethyl chloride hydrochloride (8 g.) as waxy plates, m. p. 88—89° (Found: Cl<sup>-</sup>, 10·6.  $C_{18}H_{38}NCl_2 \cdot HCl$  requires Cl<sup>-</sup>, 10·45%). For condensation with 2 : 4 : 6-trichlorophenol, a benzene solution of 2-di-*n*-octylaminoethyl chloride was prepared by stirring an aqueous suspension of the hydrochloride with an excess of sodium hydroxide solution and extracting the liberated base with benzene. After drying ( $MgSO_4$ ) the benzene solution was used without further treatment.

**2 : x : x-Tetrachloroquinoline.**—Chlorination of carbostyryl by the method of Friedlander and Weinberg (*Ber.*, 1882, **15**, 1425) gave a trichlorocarbostyryl instead of the dichlorocarbostyryl described by these authors. Carbostyryl (5 g.) was dissolved in a mixture of glacial acetic acid (100 c.c.) and concentrated hydrochloric acid (50 c.c.). The mixture was warmed gently to dissolve all solid, and potassium chlorate (10 g.) was added in small portions at ca. 60°. The solid which separated on cooling was recrystallised from glacial acetic acid, affording x : x : x-trichlorocarbostyryl as colourless needles, m. p. 217—218° (Found: C, 43·1; H, 1·6; N, 5·7.  $C_9H_4ONCl_3$  requires C, 43·4; H, 1·6; N, 5·6%). This compound (9·3 g.) was heated with phosphorus oxychloride (10 g.) and phosphorus pentachloride (20 g.) at 140—150° for 3 hours. Decomposition of the mixture with ice and water afforded 2 : x : x : x-tetrachloroquinoline (10 g.), m. p. 151°, raised to 154—155° by crystallisation from ethanol (Found: N, 5·5.  $C_9H_3NCl_4$  requires N, 5·25%).

**Preparation of  $\omega$ -Aryloxyalkylamines.**—*Method A.* The phenol dissolved in methanol was neutralised with the equivalent amount of methanolic sodium methoxide, excess of benzene was added, and the methanol removed azeotropically. 1 Mol. of the dialkylaminoalkyl chloride was then added to the benzene suspension of the sodium salt, and the mixture heated under reflux for 24 hours. The benzene was washed with dilute aqueous sodium hydroxide, and the product extracted into dilute hydrochloric acid. The oil liberated by basification of the acid extract was isolated with ether or benzene and distilled under reduced pressure.

*Method B.* Equivalent quantities of the phenol and the dialkylaminoalkyl chloride hydrochloride were boiled under reflux in methanol containing two equivalents of sodium methoxide for 12—24 hours. The methanol was distilled off, the residual oil dissolved in ether, washed with water, and purified by distillation.

*Method C.* As for method B but with ethanol instead of methanol. In general, methods B and C gave yields much inferior to method A.

*Method D.* The sodium salt, which was soluble in ether, was condensed in this solvent with diethylnitrosochloride.

*Method E.* Sodium 2 : 4 : 6-trichlorophenoxide was stirred with a large excess (4—5 mols.) of the alkylene dibromide and heated in a cyclohexanol-vapour-bath for 48 hours. Chloroform was then added, the solution washed with water, and the product distilled. The resulting  $\omega$ -(2 : 4 : 6-trichlorophenoxy)-alkyl bromide was heated under reflux with excess of diethylamine for 6 hours, the excess of diethylamine removed, and the free base liberated with aqueous sodium hydroxide and isolated with ether. It was purified either by distillation or by crystallisation of the hydrochloride.

*Method F.* The 2-chloroquinoline was boiled under reflux in a solution of sodium (1 equivalent) in excess of diethylaminoethanol for 6 hours. Excess of diethylaminoethanol was removed *in vacuo*, and the product isolated as previously.

The hydrochlorides were prepared by the addition of ethanolic hydrogen chloride to an ethereal solution of the base, followed by crystallisation from ethanol, methanol, acetone, or benzene.

*2 : 4 : 6-Trichlorophenoxyacetamidinium Chloride.*—2 : 4 : 6-Trichlorophenoxyacetic acid (12.6 g.) was heated under reflux with thionyl chloride (16 c.c.) overnight. The crude acid chloride obtained by removal of the excess of thionyl chloride was dissolved in hot benzene, and gaseous ammonia passed into the solution. After cooling, the crude amide (9.9 g.; m. p. 189—191°) was collected, dried, and heated under reflux overnight with thionyl chloride (20 c.c.). Distillation gave the crude cyanide (7.1 g.), b. p. 143—145°/2 mm., m. p. 103° after crystallisation from ethanol. The cyanide (35 g.) was dissolved in a mixture of dioxan (370 c.c.), chloroform (75 c.c.), and ethanol (22 c.c.; 2.5 mols.) and saturated at 0° with dry hydrogen chloride. After 1 week at room temperature the clear solution was concentrated to a small volume *in vacuo*. The imino-ether hydrochloride, obtained by precipitation with ether, was shaken with saturated ethanolic ammonia for 5 days. The reaction mixture was concentrated to a small volume *in vacuo* at 40° and filtered. The colourless residue was extracted with boiling 2N-hydrochloric acid (3 × 100 c.c.). The combined extracts on cooling deposited colourless needles (14 g.), m. p. 218—219° (decomp.). The mother-liquor from the above concentrate, on evaporation to dryness *in vacuo* and extraction of the residue with hot acid, afforded a further crop (4.5 g.), m. p. 214—217° (decomp.). The crude product (5 g.) was dissolved in hot water (225 c.c.), and a small amount of neutral insoluble material filtered off. Addition of concentrated hydrochloric acid to the filtrate gave 2 : 4 : 6-trichlorophenoxyacetamidinium chloride (3.23 g.) as colourless needles, m. p. 235° (decomp.) (Found: N, 9.6.  $C_8H_8ON_2Cl_4$  requires N, 9.65%). The neutral material, crystallised from ethanol or aqueous ethoxyethanol, had m. p. 193° and proved to be 2 : 4 : 6-trichlorophenoxyacetamide (Found: N, 5.3.  $C_8H_8O_2NCl_3$  requires N, 5.5%).

*2-(2 : 4 : 6-Trichlorophenoxyethyl)-4 : 5-dihydroglyoxalium Chloride.*—This was prepared by the method of Oxley and Short (B.P. 614,072). A mixture of the above amidinium chloride (7.6 g.) and ethylenediamine (3.13 g.) in absolute ethanol (25 c.c.) was kept for 10 days, whereupon most of the solid dissolved. A small amount of a crystalline high-melting (*ca.* 300—310°) by-product was filtered off and the filtrate evaporated at room temperature. The residual gum was dissolved in a minimum amount of water, and the solution filtered. Addition of concentrated hydrochloric acid gave 2-(2 : 4 : 6-trichlorophenoxyethyl)-4 : 5-dihydroglyoxalium chloride (5.5 g.) as colourless needles, m. p. 148—150°, raised to 157.5—158.5° by recrystallisation from ethanol (Found: N, 8.8.  $C_{10}H_{10}ON_2Cl_4$  requires N, 8.9%).

The authors gratefully acknowledge their indebtedness to Mr. C. E. Coulthard, Dr. L. Dickinson, and Miss B. Croshaw for the biological tests, and to Dr. W. F. Short for his interest in the work. They also thank Miss M. Birchmore and Miss F. Skidmore for carrying out the analyses.

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[Received, June 18th, 1949.]