921. *The Oxidation of Phenolic Ethers with Peroxyacetic Acid.*

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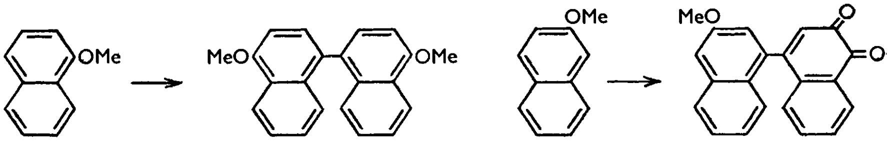
The oxidation of a number of alkyl-, halogeno-, and nitro-substituted alkyl aryl ethers has been examined. Electrophilic 1 : 4-dihydroxylation, usually with the displacement of a hydrogen atom and a methoxyl group, leads to the formation of 1 : 4-quinones. The 1 : 2-quinones formed by 1 : 2-hydroxylation are rapidly oxidised further, with opening of the aromatic ring, giving water-soluble products.

Phenols react with hydrogen peroxide and acetic acid, undergoing hydroxylation at positions activated towards electrophilic attack. Further oxidation gives 1 : 4-quinones and ring-fission products such as muconic and fumaric acids.[1]

Fernholz[2] showed that a series of alkyl phenyl ethers were oxidised by peroxybenzoic acid, absorbing 0·5—7·8 atom of oxygen, whilst 1- and 2-naphthyl ethers, in benzene, gave first 1 : 2-naphthaquinone, which then reacted with fission of the $C_{(1)}$–$C_{(2)}$ bond to give, *via* the acid anhydride, a monoether of *o*-carboxycinnamic acid. As by-products, the 1- and 2- ethers gave respectively 1 : 4-naphthaquinone and 2-alkoxy-1 : 4-naphthaquinone. The products with peroxyformic acid, however, were quite different:[3]



Friess, Soloway, Morse, and Ingersoll[4] studied the action of peroxybenzoic acid in chloroform on the methyl ethers of mono-, di-, and tri-hydric phenols. 1 : 4-Quinones were usually isolated, sometimes with the displacement of a methoxy-group. 1 : 2-Dimethoxybenzene gave dimethyl muconate only, and in other cases small amounts of oxalic acid derivatives were isolated with the quinones. The relative reactivity and position of quinone-formation were compatible with electrophilic attack upon the ring, and from a

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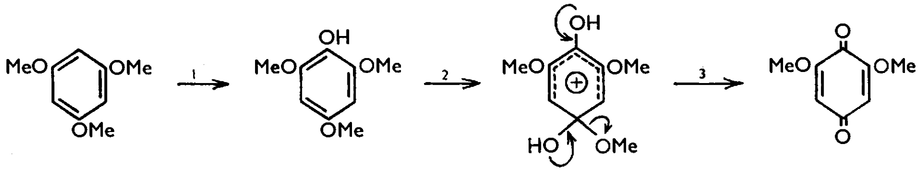
[1] Henderson and Boyd, *J.*, 1910, **97**, 1659; Böeseken and Engelberts, *Proc. Acad. Sci. Amsterdam*, 1931, **34**, 1282; 1932, **35**, 750; Grundman and Trischmann, *Ber.*, 1936, **69**, 1775; Elvidge, Linstead, and Sims, *J.*, 1951, 3386.

[2] Fernholz, *Chem. Ber.*, 1951, **84**, 110.

[3] Fernholz and Piazolo, *Ber.*, 1954, **87**, 578.

[4] Friess, Soloway, Morse, and Ingersoll, *J. Amer. Chem. Soc.*, 1952, **74**, 1305.

kinetic study of the reaction of 1 : 3 : 5-trimethoxybenzene the following mechanism was suggested.



1: $Ph{\cdot}CO_8H$, slow. 2: $Ph{\cdot}CO_3H$, fast. 3: $-MeOH, -H^+$.

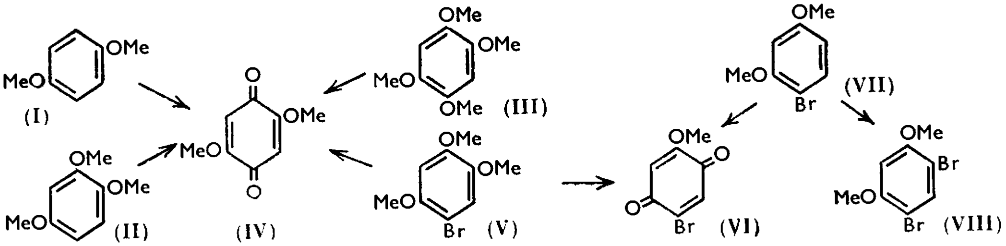
The present investigation was undertaken after it had been observed that the reaction of *p*-tolyl 2 : 4 : 6-trimethoxyphenyl sulphide with hydrogen peroxide in acetic acid gave, not the expected sulphone, but 2 : 6-dimethoxy-1 : 4-benzoquinone which was also obtained by the oxidation of 2 : 4 : 6-trimethoxydiphenylmethanol and of 1 : 3 : 5-trimethoxybenzene.[5]

A number of alkyl-, halogeno-, and nitro-substituted phenolic ethers were prepared and their products of nuclear oxidation examined.

The ether in acetic acid containing a trace of sulphuric acid was mixed with hydrogen peroxide (usually 90%). The ethers which were essentially unchanged after at least a week, or which underwent ring-fission yielding water-soluble substances, are recorded in the Experimental section. When quinones were formed the reactants and products are recorded in Table 1: new quinones were characterised by the derivatives formed on reductive acetylation (Table 2).

The ethers which did not react are those which would be expected to be less susceptible to electrophilic substitution. When oxidation did take place, only 1 : 4-quinones, never 1 : 2-, were isolated, the oxygen atoms being introduced at positions which would be expected to be susceptible to electrophilic attack. The ethers which yielded water-soluble products are again those carrying a number of electron-repelling substituents: a decrease in the concentration of the hydrogen peroxide reduced the proportion of the ether which reacted, but in no case did it permit the isolation of quinone.

Formation of Quinones.—The 1 : 4-quinones were isolated in yields of 10—30%. Usually a hydrogen atom and a methoxyl group, but occasionally two hydrogen atoms, or two methoxyl groups, were eliminated. Thus 1 : 4-dimethoxybenzene (I), 1 : 2 : 4-trimethoxybenzene (II), and 1 : 2 : 4 : 5-tetramethoxybenzene (III) all gave 2 : 5-dimethoxy-1 : 4-benzoquinone (IV).



Alkyl and halogeno-groups were not usually displaced during quinone-formation, but 1-bromo-2 : 4 : 5-trimethoxybenzene (V) was oxidised to a mixture of 2 : 5-dimethoxy-1 : 4-benzoquinone (IV) and 2-bromo-5-methoxy-1 : 4-benzoquinone (VI). In two cases, however, quinone was formed in parallel with a bromine-transfer reaction. 1-Bromo-2 : 4-dimethoxybenzene (VII) in acetic acid containing 30% (100 vol.) hydrogen peroxide, after a few days deposited a mixture of 2-bromo-5-methoxy-1 : 4-benzoquinone (VI) and 1 : 5-dibromo-2 : 4-dimethoxybenzene (VIII), both of which were stable towards the reagents

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[5] Kenyon and Mason, *J.*, 1952, 4964.

TABLE 1. *Oxidation of ethers to quinones.*

Ether	Quinone produced			Found (%)				Required (%)			
Substituents in benzene ring, or full name	Substituents in 1 : 4-benzoquinone, or full name	Appearance	M. p.	C	H	Cl/Br/ N	Formula	C	H	Cl/Br/ N	Ref.
1-Methoxy-3 : 5-dimethyl-	2 : 6-Dimethyl- (*A*)	Golden rods	72°	—	—	—	—	—	—	—	1
1 : 2-Dimethoxy-4-methyl-	2-Methoxy-5-methyl- (*B*)	Yellow rods	175—176	63·5	5·2	—	$C_8H_8O_3$	63·2	5·3	—	2
2 : 3-Dimethoxynaphthalene	2 : 3-Dimethoxy-1 : 4-naphthaquinone	Yellow needles	116—117	66·0	4·7	—	$C_{12}H_{10}O_4$	66·0	4·6	—	3
1 : 3-Dimethoxy-	2-Methoxy-5-(4-methoxy-2 : 5-benzoquinonyl)- (*C*)	Yellow rods	231—232 * [a]	61·4	3·9	—	$C_{14}H_{10}O_6$	61·3	3·7	—	
1 : 3-Dibenzyloxy-	2-Benzyloxy-5-(4-benzyloxy-2 : 5-benzoquinonyl)-	Orange rods	258 *	72·9	4·3	—	$C_{26}H_{18}O_6$	73·2	4·3	—	
1 : 3-Dimethoxy-5-methyl-	2-Methoxy-6-methyl-	Yellow plates	149—150·5	62·9	5·1	—	$C_8H_8O_3$	63·2	5·3	—	4
2 : 4-Dimethoxy-1-ethyl-	2-Ethyl-5-methoxy- (*D*)	Yellow needles	154—155	65·2	6·0	—	$C_9H_{10}O_3$	65·1	6·1	—	
1 : 3-Dimethoxynaphthalene	2-Methoxy-1 : 4-naphthaquinone (*E*)	Yellow needles	183—184	70·0	4·4	—	$C_{11}H_8O_3$	70·2	4·3	—	5
1 : 4-Dimethoxy-	2 : 5-Dimethoxy- (*F*)	Yellow leaflets	300 *	56·9	4·7	—	$C_8H_8O_4$	57·2	4·8	—	6
1 : 4-Dimethoxy-2 : 5-dimethyl-	2 : 5-Dimethyl-	Golden rods	125—126 [b]	—	—	—	—	—	—	—	
1-Methoxy-4-*p*-nitrobenzyloxy-	2-Methoxy-5-*p*-nitrobenzyloxy-	Yellow needles	252—255 *	58·4	4·3	5·0	$C_{14}H_{11}O_6N$	58·1	3·8	4·8	
1 : 2 : 3-Trimethoxy-	2 : 6-Dimethoxy-	Orange rods	252 * [c]	—	—	—	—	—	—	—	
1 : 3 : 5-Trimethoxy-	2 : 6-Dimethoxy-	Orange rods	252 * [c]	—	—	—	—	—	—	—	
1 : 2 : 4-Trimethoxy-	2 : 5-Dimethoxy- (*G*)	Orange rods	300 *	57·4	4·8	—	$C_8H_8O_4$	57·1	4·8	—	
1 : 2 : 4 : 5-Tetramethoxy-	2 : 5-Dimethoxy- (*H*)	Yellow plates	300 *	—	—	—	—	—	—	—	
1-Bromo-2 : 4-dimethoxy-	2-Bromo-5-methoxy- (*I*)	Yellow rods	190—191	39·1	2·5	36·4	$C_7H_5O_3Br$	38·7	2·3	36·8	
1-Chloro-2 : 4-dimethoxy-	2-Chloro-5-methoxy- (*J*)	Yellow needles	174	49·2	3·0	20·9	$C_7H_5O_3Cl$	48·6	2·9	20·6	
2(or 4)-Bromo-1 : 3-dimethoxy-5-methyl-	3(or 5)-Bromo-2-methoxy-6-methyl- (*K*)	Yellow needles	150—151	41·5	3·1	34·1	$C_8H_7O_3Br$	41·6	3·1	34·6	
2 : 4-Dibromo-1 : 3 : 5-trimethoxy-	2 : 6-Dibromo-3 : 5-dimethoxy- [d]	Orange plates	176—177	29·5	1·9	49·0	$C_8H_6O_4Br_2$	29·8	2·1	49·0	7
1-Bromo-2 : 4 : 5-trimethoxy-	2 : 5-Dimethoxy- (*L*)	Golden blades	300 *	57·3	4·7	—	$C_8H_8O_4$	57·2	4·8	—	
	2-Bromo-5-methoxy-	Yellow rods	189—191 * [e]	—	—	—	—	—	—	—	
2-Bromo-1 : 3 : 5-trimethoxy-	3-Bromo-2 : 6-dimethoxy-	Yellow needles	148—149	39·2	2·8	32·1	$C_8H_7O_4Br$	38·9	2·9	32·3	8
2 : 4-Dichloro-1 : 3 : 5-trimethoxy-	2 : 6-Dichloro-3 : 5-dimethoxy- [f]	Golden rods	149—150	41·0	2·7	29·1	$C_8H_6O_4Cl_2$	40·5	2·6	29·9	9
2 : 4 : 2′ : 4′-Tetramethoxydiphenyl-	2-Methoxy-5-(4-methoxy-2 : 5-benzoquinonyl)-	Yellow rods	230 [g]	—	—	—	—	—	—	—	

Notes: * With decomp. [a] Sublimes at 150° *in vacuo.* [b] And mixed with an authentic specimen. [c] And in mixture. [d] Together with an equal amount of 1 : 3 : 5-tribromo-2 : 4 : 6-trimethoxybenzene. [e] And mixed with (*I*). [f] Together with about half its weight of 1 : 3 : 5-trichloro-2 : 4 : 6-trimethoxybenzene, m. p. and mixed m. p. 112°. [g] And mixed with *C*.

[1] Nölting and Forel, *Ber.*, 1885, **18**, 2668, give m. p. 73°. [2] Luff, Perkin, and Robinson, *J.*, 1910, **97**, 1131, give m. p. 170—172°. [3] Fieser, *J. Amer. Chem. Soc.*, 1928, **50**, 439, gives m. p. 115°. [4] Heinrich and Nachtigall, *Ber.*, 1903, **36**, 889, give m. p. 147°. [5] Fieser, *J. Amer. Chem. Soc.*, 1926, **48**, 2922, gives m. p. 183·5°. [6] Anslow and Raistrick, *J.*, 1939, 1446, give m. p. 303°, and Friess *et al.*, *J. Amer. Chem. Soc.*, 1952, **74**, 1305, 220°. By heating with an ethanolic solution of stannous chloride the quinone was converted into 1 : 4-dihydroxy-2 : 5-dimethoxybenzene, m. p. 171—172·5°. Thoms and Schüller, *Arch. Pharm.*, 1907, **245**, 284, give m. p. 170°. [7] Hofmann, *Ber.*, 1878, **11**, 329, gives m. p. 175°. [8] Levine, *J. Amer. Chem. Soc.*, 1926, **48**, 797, gives m. p. 148°.

used. The original monobromo-ether (VII) reacted with more dilute peroxyacetic acid, or with dilute nitric acid, or immediately with free bromine, giving the dibromo-ether (VIII) as the only water-insoluble product, whereas more concentrated peroxy-acid gave only the quinone. It appears that bromination is probably brought about by free bromine which is formed by a ring-cleavage reaction which does not proceed through the 1 : 4-quinone. A similar halogen-transfer reaction occurs during the oxidation of 2 : 4-dibromo- and 2 : 4-dichloro-1 : 3 : 5-trimethoxybenzene, when a mixture of the corresponding 1 : 3 : 5-trihalogeno-2 : 4 : 6-trimethoxybenzene and 2 : 6-dihalogeno-3 : 5-dimethoxy-1 : 4-benzoquinone is formed.

Whereas Friess *et al.*[4] found that peroxybenzoic acid with 1 : 3-dimethoxybenzene gave 2-hydroxy-5-methoxy-1 : 4-benzoquinone, we find that with peroxyacetic acid nuclear coupling occurs to yield 2-methoxy-5-(4-methoxy-2 : 5-benzoquinonyl)-1 : 4-benzoquinone, identical with the product from 2 : 4 : 2′ : 4′-tetramethoxydiphenyl, This is similar to the nuclear coupling observed by Fernholz and Piazolo[3] and may indicate the incursion of a free-radical process, perhaps initiated by traces of metal ions. The reactions leading to quinone-formation can be accommodated in the mechanism described by Friess *et al.*[4] in which electrophilic hydroxylation at a ring atom carrying an OH or OMe group gives a structure which loses H_2O or HOMe forming the quinone carbonyl group. The 1 : 4-quinones so formed are stable under the reaction conditions and can be isolated, but the 1 : 2-quinones are readily oxidised further by a Baeyer–Villiger reaction[6] and are probably the main source of the water-soluble products.

EXPERIMENTAL

The ethers were prepared by appropriate methods; the following are new.

1-*Methoxy*-4-p-*nitrobenzyloxybenzene*.—A solution of *p*-methoxyphenol (2·5 g.), *p*-nitrobenzyl bromide (4·5 g.), and sodium hydrogen carbonate (2·5 g.) in ethanol (50 c.c.) and water (18 c.c.) was heated under reflux for 1 hr., yielding 1-*methoxy*-4-p-*nitrobenzyloxybenzene* (3·4 g.), pale yellow rods (from ethanol), m. p. 90·5—91·5° (Found: C, 64·8; H, 5·0; N, 6·1. $C_{14}H_{13}O_4N$ requires C, 64·9; H, 5·0; N, 6·2%).

2(*or* 4)-*Bromo*-1 : 3-*dimethoxy*-5-*methylbenzene*.—A solution of orcinol dimethyl ether (25 g.) and *N*-bromosuccinimide (20 g.) in carbon tetrachloride (150 c.c.) was heated on the steam-bath for 10 hr. The resultant *bromo-ether*, b. p. 112—120°/21 mm. (16 g.), separated from methanol in fern-like needles, m. p. 49—50° (Found: C, 46·5; H, 4·7; Br, 34·2. $C_9H_{11}O_2Br$ requires C, 46·8; H, 4·8; Br, 34·6%).

1-*Chloro*-2 : 4-*dimethoxybenzene*.—A solution of 1-chloro-2 : 4-dihydroxybenzene in sodium hydroxide was shaken with dimethyl sulphate, giving the *chloro-ether*, b. p. 238° (Found: C, 61·2; H, 5·7; Cl, 22·2. $C_8H_9O_2Cl$ requires C, 61·3; H, 5·7; Cl, 22·7%).

2 : 4-*Dichloro*-1 : 3 : 5-*trimethoxybenzene*.—Chlorine from potassium permanganate (6·3 g.) and hydrochloric acid was led into 1 : 3 : 5-trimethoxybenzene (8·4 g.) in acetic acid (50 c.c.). The yellow crystals, after being washed with sodium hydroxide, were crystallised from butanol giving 2 : 4-*dichloro*-1 : 3 : 5-*trimethoxybenzene* (6 g.) as glistening plates, m. p. 155° (Found: C, 45·4; H, 4·1; Cl, 29·7. $C_9H_{10}O_3Cl_2$ requires C, 45·6; H, 4·2; Cl, 30·0%).

Oxidation of Phenolic Ethers to Quinones.—General procedure. To a solution of the ether in glacial acetic acid (5—15 parts) containing sulphuric acid (1—4 drops) was added somewhat more than the calculated amount of hydrogen peroxide (generally 90%, but sometimes as low as 30%, depending on the vigour of the reaction) if necessary drop by drop and with external cooling. After several days the separation of yellow crystals of the quinone appeared to be complete; in a few cases dilution with water proved necessary.

Results are given in Table 1 and those obtained by the reductive acetylation of the quinones in Table 2.

1-*Bromo*-2 : 4-*dimethoxybenzene*. The ether (5 g.) in acetic acid (60 c.c.) and hydrogen peroxide (40 c.c. of 30%) after a week had deposited a mixture of colourless and bright red crystals (3 g.). These were separated in two ways: (i) Warming with dilute sodium hydroxide

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[6] Hassal, *Organic Reactions*, 1957, **9**, **73**.

dissolved the red quinone leaving the colourless 1 : 5-dibromo-2 : 4-dimethoxybenzene which separates from ethanol in needles, m. p. 142—143° alone or mixed with an authentic specimen. (ii) Extraction with boiling *cyclo*hexane left undissolved 2-bromo-5-methoxy-1 : 4-benzoquinone, rosettes of golden rods, m. p. 190—191° (cf. Tables 2 and 3). The dibromo-derivative and the quinone were produced in the ratio 2 : 1.

TABLE 2. *Reductive acetylation of quinones.*

Reductive acetylation is effected by heating the quinone (1 g.) with acetic anhydride (3 c.c.) and zinc dust (1 g.) and a few drops of pyridine. It converts a 1 : 4-quinone into the corresponding derivative of 1 : 4-diacetoxybenzene; for example, 2 : 6-dimethyl-1 : 4-benzoquinone (*A*) gives 2 : 5-diacetoxy-1 : 3-dimethylbenzene.

	Product of reductive acetylation								
			Found (%)				Required (%)		
Quinone	Appearance	M. p.	C	H	Cl/Br	Formula	C	H	Cl/Br
A	Glassy leaflets	92—93°	65·1	6·2	—	$C_{12}H_{14}O_4$	64·9	6·4	—
B	Prismatic rods	129—130	60·0	6·1	—	$C_{12}H_{14}O_5$	60·4	5·9	—
C	Long rhombs	187—187·5	59·3	5·1	—	$C_{22}H_{22}O_{10}$	59·2	5·0	—
D	Silky needles	112—113	62·3	6·3	—	$C_{13}H_{16}O_5$	61·9	6·4	—
E	Plates	130—131·5 [a]	—	—	—	—	—	—	—
F, G *H, L*	Glassy rhombs	182·5—183·5	56·5	5·6	—	$C_{13}H_{16}O_7$	56·7	5·6	—
I	Prismatic rods	136—137	44·1	4·1	25·8	$C_{11}H_{11}O_5Br$	43·6	3·7	26·4
J	Rhombs	127	51·5	4·3	13·8	$C_{11}H_{11}O_5Cl$	51·1	4·3	13·7
K	Glassy plates	133—134	45·7	4·4	24·9	$C_{12}H_{13}O_5Br$	45·4	4·1	25·2

[a] Fieser, *J. Amer. Chem. Soc.*, 1926, **48**, 2922, gives m. p. 129—130°.

From the mother-liquor there were obtained, by dilution and extraction, additional amounts of the dibromo-derivative (0·6 g.) and the quinone (0·3 g.) together with a highly unsaturated, water-soluble oil (2·4 g.) from which no crystalline derivative could be obtained. A few mg. of oxalic acid (as oxaldi-*p*-toluidide, m. p. 270—272° alone or mixed) were isolated.

Nitric acid (5 c.c.) was added to a solution of the bromo-ether (3 g.) in acetic acid (10 c.c.): the resulting green solution, when diluted with water, deposited a greenish solid from which 1 : 5-dibromo-2 : 4-dimethoxybenzene (1·7 g.), but no quinone, was obtained by recrystallisation from ethanol.

Ethers which are non-reactive towards peroxyacetic acid. The following ethers were recovered after treatment with peroxyacetic acid: 1 : 2-dimethoxybenzene, 1-methoxy-2-methylbenzene, 1-methoxy-4-methylbenzene, 1-bromo-4-methoxybenzene, 1-methoxy-4-phenylbenzene, 1-methoxy-3 : 5-dimethylbenzene, 1-bromo-3-methoxy-4-methylbenzene, 1-chloro-3-methoxy-4-methylbenzene, 2-chloro-5-methoxy-1: 3-dimethylbenzene, 1-chloro-2-methoxy-3-phenylbenzene, 2-methoxy-1 : 3-dimethylbenzene, 1-methoxy-4-phenoxybenzene, ?-bromo-1 : 2-dimethoxy-4-methylbenzene, 2-chloro-1 : 4-dimethoxybenzene, 1 : 4-dimethoxy-2-methylbenzene, 1 : 4-dimethoxy-2-phenoxybenzene, 1 : 2-dimethoxy-4-nitrobenzene, 2 : 4-dimethoxy-1-nitrobenzene, 1 : 3-dimethoxy-2-*p*-nitrobenzyloxybenzene, 1 : 4-dimethoxynaphthalene, 1 : 4-diphenoxybenzene, 1 : 2 : 3-tribromo-4 : 5 : 6-trimethoxybenzene, and 4 : 4′-dimethoxydiphenyl ether.

Ethers which are oxidised to water-soluble products. The following ethers gave only water-soluble products after treatment with peroxyacetic acid: methoxybenzene, 1-methoxy-3-methylbenzene, 2-methoxy-1 : 4-dimethylbenzene, 4-methoxy-1 : 2-dimethylbenzene, 1-methoxy-3-hydroxybenzene, 1-methoxy-4-hydroxybenzene, 1 : 4-dimethoxy-2-bromobenzene, 2 : 7-dimethoxynaphthalene, and 1 : 5-dimethoxynaphthalene.

Thanks are expressed to the Central Research Funds Committee of London University for a Grant.

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BRITISH OXYGEN RESEARCH AND DEVELOPMENT LTD.,
DEER PARK ROAD, LONDON, S.W.19.

[*Received, August 8th*, 1958.]