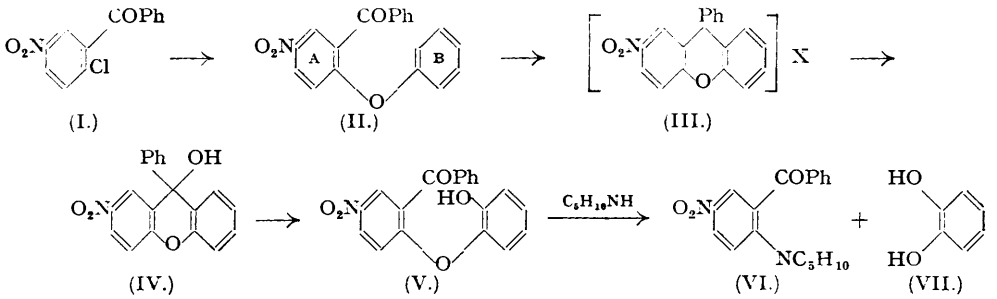
13. ortho-*Hydroxylation of Phenols. A New Case of the Smiles Rearrangement.*

By J. D. Loudon, J. R. Robertson, J. N. Watson, and (in part) (Miss) S. D. Aiton.

The potassium salts of various phenols condense with 2-chloro-5-nitrobenzophenone to form 5-*nitro*-2-*aryloxybenzophenones* which with concentrated sulphuric acid afford solutions of the corresponding 9-phenylxanthylium sulphates. These solutions yield (*a*) derivatives of 9-phenylxanth-hydrol when treated with water, or (*b*) 5-*nitro*-2-o-*hydroxyaryloxybenzophenones*, *e.g.*, (V), when treated with acetic acid and hydrogen peroxide. Compounds of type (V) react with piperidine to give catechol derivatives and 5-*nitro*-2-*piperidinobenzophenone*, form unstable, covalent sodium derivatives, and in particular cases rearrange in alkaline solution, the nitrobenzophenone residue migrating to the second oxygen atom of the catechol system, *e.g.*, (X) ⟶ (XI).

The following investigation was undertaken to test the practicability of the reaction scheme illustrated by (I)—(VII) and to define the respects requiring particular study in order to achieve a general development. Condensation between 2-chloro-5-nitrobenzophenone (I) and the potassium salts of various phenols afforded the aryl *ethers*, *e.g.*, (II), in satisfactory yields and, in most cases, these were converted smoothly into 9-phenylxanthylium salts by dissolution in cold concentrated sulphuric acid. The corresponding *xanth-hydrols*, *e.g.*, (IV), were obtained by pouring the solutions into water. This cyclisation process is analogous to that already described for the formation of thioxanthen derivatives (Loudon *et al.*, *J.*, 1941, 747) and, since it depends on nucleophilic reactivity in ring B [cf. (II)], was less readily accomplished in cases where this ring was nitrated.

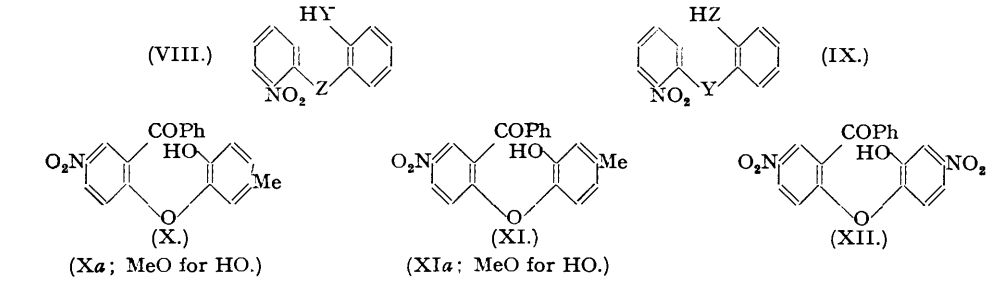


Quint and Dilthey (*Ber.*, 1931, **64**, 2082) have shown that 9-phenylxanthylium perchlorate is oxidised by hydrogen peroxide in acetic acid to 2-*o*-hydroxyphenoxybenzophenone (V; H for (NO_2). Similar oxidation of *perchlorates* derived from our 2-nitro-9-phenylxanth-hydrols gave mainly neutral products, presumably *peroxides* of the type encountered by Dilthey (*loc. cit.*). In a number of cases, however, the required catechol derivatives, *e.g.*, (V), were very readily obtained by oxidising the xanth-hydrol in sulphuric–acetic acid, and the process gave excellent results with 9-phenylxanth-hydrol itself. Consequently, in these cases a simple and almost quantitative conversion of the phenol derivatives (II; ring B = phenyl, or *o*-, *m*-, or *p*-tolyl) into the catechol derivatives, *e.g.*, (V), was achieved by dissolving the former in concentrated sulphuric acid, diluting the solution with acetic acid and adding hydrogen peroxide. That the pyrylium ring opens in the sense shown was confirmed by the identity of the methylation product of (V) with the condensation product obtained from (I) and guaiacol.

The final stage of the reaction scheme, *viz.*, liberation of the catechol from its aryl ether, was not examined extensively. The scission of *o*- or *p*-nitrated diaryl ethers by means of piperidine is well known (Le Fèvre, Saunders, and Turner, *J.*, 1927, 1168; Groves, Turner, and Sharp, *J.*, 1929, 512) and we have limited our present inquiry to a few test cases using this reagent. Catechol, 3 : 4-dihydroxytoluene, and 4-hydroxy-3-methoxytoluene were isolated from (V), (XI), and (XI*a*), respectively, and in each case 5-*nitro*-2-*piperidinobenzophenone* was also produced.

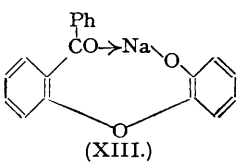
Since it is part of our project to study the extension of the process through renewed cyclisation at the catechol stage (V), with or without alkylation of the free phenolic group, it became necessary to examine the behaviour of the catechol derivatives particularly towards alkaline reagents. Smiles and his collaborators have shown (for summary and references, cf. *Ann. Reports*, 1939, **36**, 197) that the different donor-capacities in dissimilar atoms Y and Z

constitute an important factor in the rearrangement of (VIII) to (IX). Different donor-capacities will also exist where Y and Z represent atoms of the same element dissimilarly situated in the molecule. This condition and other essential features for rearrangement are present in the isomers (X) and (XI). Experiment indeed showed that when (X) was dissolved in aqueous alkali it was almost completely rearranged to the compound which had already been obtained by hydroxylating the *p*-tolyl ether (II; ring B = *p*-tolyl) and which, accordingly, has the formula (XI). For this reason also methylation of either (X) or (XI) by methyl sulphate in alkali afforded the same *methyl ether* (XI*a*), which was identified by scission with piperidine to



4-hydroxy-3-methoxytoluene as already mentioned. On the other hand, methylation without rearrangement was effected by means of diazomethane, which gave (X*a*) and (XI*a*) from (X) and (XI), respectively, the *ether* (X*a*) being identified by its formation from (I) and 3-hydroxy-4-methoxytoluene. There was also evidence of rearrangement in the case of the *nitrocatechol* derivative (XII) which was prepared from *p*-nitrophenol *via* 2 : 7-*dinitro*-9-*phenylxanth-hydrol*. The compound appeared to be isomerised by dissolution in alkali and the same change, displayed as a double melting point, occurred on heating the substance in soft-glass but not in hard-glass tubes. Unfortunately, synthesis of the compound, which would be expected as rearrangement product of (XII), was prevented by the difficulty of effecting the cyclisation step (II) ⟶ (III) where ring B contains a *m*-nitro-substituent. Nitration of (I) yielded 2-*chloro*-3′ : 5-*dinitrobenzophenone* from which by condensation with *m*- and *p*-cresol, followed by hydroxylation, there were prepared respectively 3′ : 5-*dinitro*-2-(2-*hydroxy*-5-*methylphenoxy*)- and 3′ : 5-*dinitro*-2-(2-*hydroxy*-4-*methylphenoxy*)-*benzophenone*. In alkaline solution the former of these compounds was isomerised to the latter, corresponding with the rearrangement of (X) to (XI). It is probable that in the cases examined rearrangement is not complete but reaches an equilibrium point. This is suggested by the fact that the products of rearrangement, like the synthetic samples when recovered from solution in alkali, melt lower and less sharply than the pure compounds.

In the course of these experiments in alkaline media it was noted that the sodium and potassium salts of the catechol derivatives of type (V) were only sparingly soluble in aqueous alkali. Further examination showed that in these compounds the metal is present in the covalent condition. The compounds were obtained as yellow crystalline solids of low melting points; they were sparingly soluble in cold water and were hydrolysed to the metal-free compounds by warm water; they dissolved readily in warm benzene or chloroform, losing water and giving orange-coloured solutions from which less coloured, lower hydrated forms separated on cooling. Their general instability made it difficult to secure consistent and reliable analytical data. Quint and Dilthey (*loc. cit.*) describe a yellow sodium salt of 2-(*o*-hydroxyphenoxy)benzophenone and re-examination of this compound showed that here too the metal is covalently bound. Since corresponding salts of 2-hydroxydiphenyl ether are of the normal type, the carbonyl group of the present compounds appears to take part in the covalent linking of the metal. By analogy with the covalent alkali derivatives of salicylideneacetophenone and related compounds investigated by Smiles and his colleagues (cf. Dvorkovitz and Smiles, *J.*, 1938, 2022), this suggests a structure such as (XIII) containing a strainless 9-membered ring. It is noteworthy, however, that these authors were unable to find evidence of stable ring structures of this type containing more than eight members.



(XIII.)

Experimental.

2-*Chloro*-3′ : 5-*dinitrobenzophenone*.—Solutions of 2-chloro-5-nitrobenzophenone (4·4 g.) (Fries, *Annalen*, 1927, **454**, 287) and potassium nitrate (1·7 g.) in the requisite quantity of concentrated

sulphuric acid were mixed and, after 12 hours at room temperature, the mixture was poured into ice-water. The *product* formed colourless plates, m. p. 177°, from acetic acid (Found: C, 51·0; H, 2·3; N, 9·3. $C_{13}H_7O_5N_2Cl$ requires C, 50·9; H, 2·3; N, 9·1%).

For the preparation of the aryloxybenzophenones the chloronitrobenzophenone (1 mol.) was added to a fused mixture of the appropriate phenol (1—2 mols.) and its potassium salt (1·2 mols.). Gentle heating initiated an exothermic reaction which was allowed to complete itself and after further brief heating (in all 15—20 minutes) the mass was cooled and treated with a dilute solution of sodium hydroxide. The solidified product was crystallised from acetic acid, diluted if necessary. In this way the tabulated compounds were prepared from 2-chloro-5-nitrobenzophenone or from 2-chloro-3′ : 5-dinitrobenzophenone.

Aryl group.	M. p.	Formula.	Found, %. C.	Found, %. H.	Required, %. C.	Required, %. H.
5-Nitro-2-aryloxybenzophenones.						
Phenyl	150°	$C_{19}H_{13}O_4N$	71·8	4·3	71·5	4·1
o-Tolyl	121—122	$C_{20}H_{15}O_4N$	72·2	4·3	72·1	4·5
m-Tolyl	106	$C_{20}H_{15}O_4N$	72·0	4·6	72·1	4·5
p-Tolyl	129	$C_{20}H_{15}O_4N$	72·1	4·3	72·1	4·5
o-Methoxyphenyl	132	$C_{20}H_{15}O_4N$	72·0	4·5	72·1	4·5
m-Chlorophenyl	117	$C_{19}H_{12}O_4NCl$	64·9	3·5	64·5	3·4
p-Chlorophenyl	118	$C_{19}H_{12}O_4NCl$	64·8	3·3	64·5	3·4
m-Nitrophenyl	116—117	$C_{19}H_{12}O_6N_2$	62·8	3·5	62·6	3·3
p-Nitrophenyl	106	$C_{19}H_{12}O_6N_2$	62·6	3·2	62·6	3·3
2-Methoxy-5-methylphenyl	120	$C_{21}H_{17}O_5N$	69·7	4·8	69·4	4·7
β-Naphthyl	137—138	$C_{23}H_{15}O_4N$	74·75	4·2	74·8	4·1
3′ : 5-Dinitro-2-aryloxybenzophenones.						
Phenyl	73	$C_{19}H_{12}O_6N_2$	62·3	3·7	62·6	3·3
m-Tolyl	123	$C_{20}H_{14}O_6N_2$	63·8	3·6	63·5	3·7
p-Tolyl	184	$C_{20}H_{14}O_6N_2$	63·5	3·8	63·5	3·7

2-*Nitro*-9-*phenylxanth-hydrol* (IV), m. p. 184° [from benzene–petroleum (b. p. 60—80°)] (Found: C, 71·55; H, 4·1. $C_{19}H_{13}O_4N$ requires C, 71·5; H, 4·1%), was prepared by dissolving 5-nitro-2-phenoxybenzophenone in cold concentrated sulphuric acid and, after an hour at room temperature, pouring the red solution into ice-water. The *xanthylium perchlorate*, m. p. 211° (Found: C, 56·7; H, 3·4. $C_{19}H_{12}O_3N{\cdot}ClO_4$ requires C, 56·7; H, 3·0%), was obtained as orange-red crystals when perchloric acid (0·11 g.) was added to a warm solution of the xanth-hydrol (0·2 g.) in acetic acid (5·5 c.c.).

In similar fashion the following were prepared from the appropriate 5-nitro-2-aryloxybenzophenone: 2-*nitro*-9-*phenyl*-6-*methylxanth-hydrol*, m. p. 186° (Found: C, 72·2; H, 4·5. $C_{20}H_{15}O_4N$ requires C, 72·1; H, 4·5%); 2-*nitro*-9-*phenyl*-7-*methylxanth-hydrol*, m. p. 163° (Found: C, 72·1; H, 4·7. $C_{20}H_{15}O_4N$ requires C, 72·1; H, 4·5%) [the derived *perchlorate* had m. p. 260° (decomp.) (Found: C, 57·5; H, 3·5. $C_{20}H_{14}O_3N{\cdot}ClO_4$ requires C, 57·7; H, 3·6%)]; 2-*nitro*-9-*phenyl*-7 : 8-*benzxanth-hydrol*, m. p. 240° (Found: C, 74·6; H, 4·3. $C_{23}H_{15}O_4N$ requires C, 74·8; H, 4·1%); and 2 : 7-*dinitro*-9-*phenylxanth-hydrol*, m. p. 194—195° (Found: C, 62·8; H, 3·2. $C_{19}H_{12}O_6N_2$ requires C, 62·6; H, 3·3%). Cyclisation in the last case was completed by heating a solution of the ketone (2 g.) in concentrated acid (25 c.c.) at 120—130° for 20 minutes, but even these conditions failed to achieve a satisfactory cyclisation with 5-nitro-2-*m*-nitrophenoxybenzophenone which was recovered largely unchanged although the red colour of the solution indicated partial formation of the xanthylium salt.

2-o-*Hydroxyphenoxybenzophenone.*—A solution of 9-phenylxanth-hydrol (1 g.) in concentrated sulphuric acid (1 c.c.) was diluted with acetic acid (11 c.c.), and hydrogen peroxide was added dropwise and with shaking. The initial yellow colour of the solution rapidly changed to orange-red which gradually faded to a pale yellow (*ca.* 1 hour). At this stage the mixture, in which some colourless flaky crystals appeared, was poured into water. The partly solid gum solidified when rubbed with ethanol, yielding 2-*o*-hydroxyphenoxybenzophenone (0·95 g.), m. p. 103—104°, from ethanol (Quint and Dilthey, *loc. cit.*, give m. p. 104°).

Sodium derivative. The above compound dissolved in warm dilute sodium hydroxide to form a yellow solution from which, on cooling, the sodium salt separated as beautiful yellow leaflets (Found: C, 53·8; H, 5·8. Calc. for $C_{19}H_{13}O_3Na,6H_2O$: C, 54·3; H, 5·95%). When slowly heated these sintered at 80—90° and melted quite sharply at 135—136°; when suddenly exposed to a temperature of 100—110° they rapidly liquefied, re-solidified, and again melted at 135°. They appeared to be insoluble in cold water but when shaken with warm water gave first a turbid and then a clear solution from which, on cooling, needles of the parent compound, m. p. and mixed m. p. 102—104°, were deposited. On the other hand, when heated with benzene they dissolved, water being liberated, and the hot filtered solution deposited the *trihydrate* as a mass of fine colourless needles which gave a clear yellow melt at 135—136° and did not melt when plunged into a bath at 110° (Found: C, 62·9; H, 4·8. $C_{19}H_{13}O_3Na,3H_2O$ requires C, 62·3; H, 5·2%).

5-*Nitro*-2-o-*hydroxyphenoxybenzophenone* (V).—(i) A suspension of 5-nitro-9-phenylxanthylium perchlorate (1 g.) in acetic acid (10 c.c.) was treated with 30% hydrogen peroxide (2 c.c.). The colour of the salt was gradually discharged and after 12 hours at room temperature the colourless crystalline solid (*A*) was collected, and the filtrate, on dilution with water gave a flocculent precipitate. The latter, which was completely soluble in dilute sodium hydroxide, afforded the compound (V) (cf. below), and was converted by reaction with methyl sulphate in alkaline solution into 5-nitro-2-*o*-methoxyphenoxybenzophenone, m. p. and mixed m. p. 130—132°. The crystalline solid (*A*), which was the main product of the reaction, was insoluble in cold dilute alkali, liberated iodine from a solution of

potassium iodide and was probably a *peroxide* derived from the xanth-hydrol (cf. Quint and Dilthey, *loc. cit.*); it had m. p. 180° (decomp.) (from acetic acid) (Found: C, 68·1; H, 4·2. $C_{19}H_{13}O_5N$ requires C, 68·1; H, 3·9%). (ii) 5-Nitro-2-phenoxybenzophenone (2·6 g.) was dissolved in cold concentrated sulphuric acid (4·2 c.c.) and, after 30 minutes, acetic acid (26 c.c.) was added. With vigorous stirring but without external cooling, hydrogen peroxide (6 c.c.) was then added fairly rapidly (5 minutes) and the whole was kept at room temperature for 3 hours. The mixture was then poured into water, giving the required *product* (V) in almost quantitative yield. It formed faintly yellow needles, m. p. 159°, from ethanol (Found: C, 68·2; H, 4·1. $C_{19}H_{13}O_5N$ requires C, 68·1; H, 3·9%).

5-*Nitro*-2-(2-*hydroxy*-4-*methylphenoxy*)*benzophenone* (XI) was similarly obtained (i) from 2-nitro-7-methylxanthylium perchlorate which also yielded mainly a *peroxide*, m. p. 210° (decomp.) (Found: C, 69·0; H, 4·3. $C_{20}H_{15}O_5N$ requires C, 68·8; H, 4·3%), and (ii) from 5-nitro-2-*p*-tolyloxybenzophenone. It formed pale yellow needles, m. p. 150°, from ethanol (Found: C, 68·8; H, 4·2. $C_{20}H_{15}O_5N$ requires C, 68·8; H, 4·3%), and yielded 5-*nitro*-2-(2-*methoxy*-4-*methylphenoxy*)*benzophenone* (XI*a*) as colourless needles, m. p. 100—101° (from methanol) (Found: C, 69·8; H, 4·8. $C_{21}H_{17}O_5N$ requires C, 69·4; H, 4·7%), when methylated either with diazomethane in ether or with methyl sulphate in aqueous sodium hydroxide. By acidifying solutions of (XI) in aqueous or ethanolic potassium hydroxide, which had been kept at room temperature for periods up to 5 days, the compound was recovered mainly unchanged, although the m. p. and mixed m. p. 145—148° was invariably lower even after crystallisation.

5-*Nitro*-2-(2-*hydroxy*-5-*methylphenoxy*)*benzophenone* (X), m. p. 158° (Found: C, 68·9; H, 4·1. $C_{20}H_{15}O_5N$ requires C, 68·8; H, 4·3%), and 5-*nitro*-2-(2-*hydroxy*-6-*methylphenoxy*)*benzophenone*, m. p. 127—128° (Found: C, 68·7; H, 4·4%), were similarly prepared from the appropriate 5-nitro-2-aryloxybenzophenones. When solutions of (X) in acetone and diazomethane in ether were mixed and kept at room temperature for 2 days, concentration of the resulting solution afforded 5-nitro-2-(2-methoxy-5-methylphenoxy)benzophenone (X*a*), m. p. and mixed m. p. 120° (from ethanol), whereas methylation of (X) with methyl sulphate in dilute sodium hydroxide gave (XI*a*), m. p. and mixed m. p. 100—101°. Acidification of a solution of (X) in 5% aqueous potassium hydroxide, which had been kept at room temperature for 24 hours, gave a phenolic product, m. p. 145—147° (from ethanol), unchanged by admixture with (XI) but depressed to m. p. 130—134° by admixture with (X).

5-*Nitro*-2-(4-*nitro*-2-*hydroxyphenoxy*)*benzophenone*.—A solution of 2 : 7-dinitro-9-phenylxanth-hydrol (0·7 g.) in concentrated sulphuric acid (3 c.c.) was treated successively with acetic acid (6 c.c.) and 30% hydrogen peroxide (1·5 c.c.) and the whole was kept at 40° for 1 hour. After addition to water the solid was collected and extracted with 90% ethanol, leaving an unidentified insoluble residue, m. p. 265° (Found: C, 63·5; H, 3·0%). On cooling (charcoal), the solution deposited colourless needles, m. p. 168—170° when determined in quartz or Jena-glass capillary tubes, but sintering at 166° and melting at *ca.* 200° in tubes of soft glass (Found: C, 60·2; H, 3·3. $C_{19}H_{12}O_7N_2$ requires C, 60·0; H, 3·2%). The *compound* was readily soluble in dilute alkali, acidification yielding a solid, which formed long colourless needles, m. p. 208—210° (quartz), from ethanol (Found: C, 60·1; H, 3·1%). The change in m. p. is probably due to rearrangement to 5-nitro-2-(5-nitro-2-hydroxyphenoxy)benzophenone but attempts to confirm this by methylation with diazomethane gave in each case a gummy product which resisted crystallisation.

3′ : 5-*Dinitro*-2-(2-*hydroxy*-4-*methylphenoxy*)*benzophenone*, m. p. 203° (from acetic acid) (Found: C, 61·0; H, 3·5. $C_{20}H_{14}O_7N_2$ requires C, 60·9; H, 3·35%), and 3′ : 5-*dinitro*-2-(2-*hydroxy*-5-*methylphenoxy*)*benzophenone*, m. p. 162° (from methanol) (Found: C, 61·1; H, 3·5%), were prepared in the usual way from 5-nitro-2-*p*- and -*m*-tolyloxybenzophenone respectively (0·5 g.) in concentrated sulphuric acid (2 c.c.) and acetic acid (5 c.c.) by warming with 30% hydrogen peroxide at 40°. The latter product was converted into the former, m. p. and mixed m. p. 201—202°, by dissolution in, and recovery from, dilute potassium hydroxide.

Scissions with Piperidine.—(i) A solution of 5-nitro-2-*o*-hydroxyphenoxybenzophenone (V) in piperidine was heated under reflux for 1 hour. After cooling and addition of benzene, the resulting solution was washed with dilute sulphuric acid and then with dilute sodium hydroxide. Acidification of the alkaline extract and recovery in ether afforded catechol, m. p. and mixed m. p. 103—104°, after distillation (diacetate, m. p. and mixed m. p. 63°). Concentration of the dried benzene solution gave 5-*nitro*-2-*piperidinobenzophenone* (VI), m. p. 100° (from ethanol), identical with a specimen prepared from (I) and piperidine (Found: N, 9·2. $C_{18}H_{18}O_3N_2$ requires N, 9·0%).

(ii) 5-Nitro-2-(2-hydroxy-4-methylphenoxy)benzophenone (XI) when similarly treated with piperidine afforded (VI) and 3 : 4-dihydroxytoluene. The latter was obtained as a red oil after acidication of the alkaline extract and recovery from ether; it afforded a solid distillate, m. p. 64°, and with bromine in acetic acid gave the tribromo-derivative, m. p. 158—160° (Ono and Imoto, *Bull. Soc. Chem. Japan*, 1936, **11**, 127, give m. p. 158°).

(iii) 5-Nitro-2-(2-methoxy-4-methylphenoxy)benzophenone (XI*a*) likewise yielded (VI) and 4-hydroxy-3-methoxytoluene. The latter was obtained as a pale yellow oil of characteristic odour and giving with ferric chloride in ethanol the blue and green colour reactions mentioned by de Vries (*Rec. Trav. chim.*, 1909, **28**, 276); with picric acid in ethanol it afforded orange-red needles of the picrate, m. p. 98—99° (from aqueous ethanol) (Beilstein records m. p.s 96°, 96·8°, and 112°).

Micro-analyses were carried out by Mr. J. M. L. Cameron.

THE UNIVERSITY, GLASGOW. [*Received, September 22nd*, 1949.]