352. *Intramolecular Substitution as a Means of comparing Activating and Deactivating Effects.*

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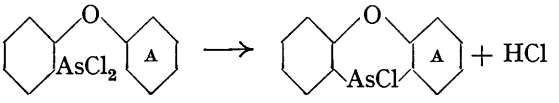
The effect of substitution on the reactivity of the aromatic nucleus can be studied, not only by nitration experiments, but also by ring-closures. The conversion of a number of substituted *o*-phenoxyphenyldichloroarsines into 10-chlorophenoxarsines has been investigated, and the rate of cyclisation correlated with the nature and position of the substituents.

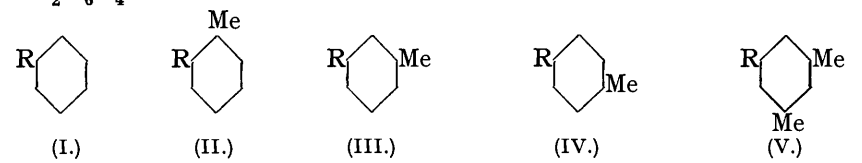
THE greater part of our knowledge of the activating or deactivating effect of substituents in the aromatic nucleus has been gained from a study of nitration, halogenation, etc. In most of these processes, the molecule under investigation may be attacked by one of many reagent molecules present in its vicinity, and the condition necessary for a reaction to take place is the activation or the polarisation of one or both of the reacting molecules. It is clearly desirable that other types of reactions should be examined, for example, those involving substitution through ring-closure, in which two parts of the same molecule react together.

It was shown by Roberts and Turner (J., 1925, **127**, 2004) that the conversion of phenoxyphenyldichloroarsine and its chloro-derivatives into chlorophenoxarsines could be

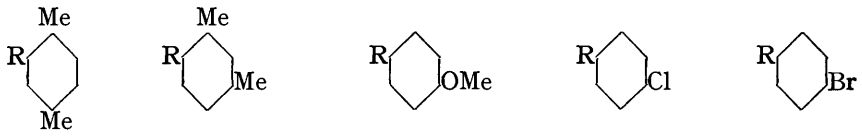


followed by determining the amount of hydrogen chloride produced during definite intervals of time, and it was found that substitution in nucleus (A) by a chlorine atom materially impeded ring-closure, the effect being greater when the chlorine was ortho or para to the oxygen atom than when it was meta. This was what would be expected.

In that work the results were only intended to be qualitative, but we have now studied the method further, mainly with new dichloroarsines, and find that it gives reproducible results, the first-order reaction equation giving reasonably trustworthy values for velocity constants, although with some of the slower reactions there was a brief period of induction, and rate constants in these cases only have a semi-quantitative significance. Ring-closure has been followed at different temperatures by using the following compounds, in which R = *o*-$AsCl_2 \cdot C_6H_4 \cdot O$—



(I.) (II.) (III.) (IV.) (V.)



(VI.) (VII.) (VIII.) (IX.) (X.)

The results obtained are summarised below, the figures referring to $k \times 10^4$ (mins.$^{-1}$) (t = temperature).

Dichloroarsine.	t = 150°.	t = 160°.	t = 175°.	t = 180°.	t = 190°.	t = 200°.	t = 210°.
I	—	13	—	40	—	97	140
II	6	18	40	47	—	120	—
III	—	100	160	230	—	—	—
IV	12	30	74	110	—	270	—
V	100	170	—	600	—	—	—
VI	48	70	—	140	—	—	—
VII	—	24	—	66	—	165	—
VIII	—	—	—	61	83	110	—
IX	—	—	—	—	9·5	17	33
X	—	—	—	—	10	19	45

The interpretation of the results is perhaps simpler than that of the results of ordinary substitution processes, since the positions in which substitution can occur are limited, and there is no doubt as to the structure of the " reagent." As to the mechanism of ring-closure, it is probable that the As–Cl bond becomes polarised, the cyclisation process then resolving itself into the attack of the electrophilic reagent, $\cdot\overset{\delta+}{As}\overset{\delta-}{Cl_2}$, on the opposed aromatic nucleus.

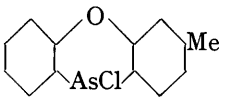
The results show that this " internal " electrophilic reagent places activated and deactivated centres in aromatic systems in the same order as that given by an external reagent such as nitric acid. For instance, all the monomethyl compounds (II—IV) are more easily cyclised than the parent dichloroarsine (I). Moreover, (III) is much more readily cyclised than (IV) and the latter is much more readily cyclised than (II), which, in turn, is more rapidly cyclised than (I) in spite of the decreased number of possible fruitful collisions. That this factor does influence rate of ring-closure is clear from a comparison of (II) and (IV), in which the activation by methyl of the reacting position or positions is approximately equal, (II) however having only half as many chances as (IV) of collision between the reacting atoms.

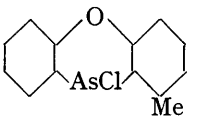
The great reactivity of the dimethyl derivative (V) is to be expected. The greater speed of cyclisation of (VI) than of (VII) is interesting in comparison with the sulphonation of *p*- and *m*-xylenes. When the reagent, as in sulphonation, can choose its target, the *m*-xylene structure is the more reactive, but when it cannot, as in the present cyclisation, the *p*-xylene structure is the more readily attacked.

The inability of a mesomeric effect to activate the *m*-position should mean a comparatively slight difference between the rate of cyclisation of (I) and of its *p*-methoxy-derivative (VIII). Actually, the latter is slightly the more reactive.

The results for compounds (IX) and (X) clearly show the deactivating effect of chlorine and bromine. Here again, cyclisation has to occur at those points which are unaffected by the mesomeric process but are subjected to the permanent effect due to induction. It is perhaps for this reason that chlorine and bromine produce almost equal deactivating effects in these compounds. It is known (Groves and Sugden, J., 1935, 973) (compare Sutton, *Proc. Roy. Soc.*, **1931**, **133**, *A*, 668) that the dipole moments of chloro- and bromo-benzene are almost identical.

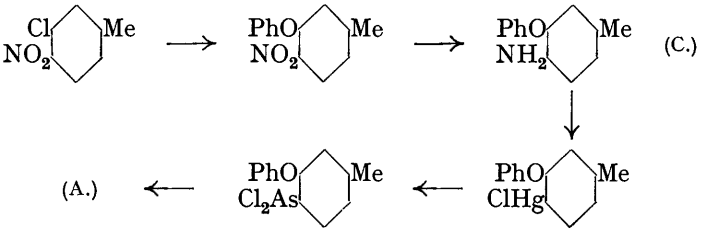
The constitution of all phenoxarsines produced by ring-closure follows from their method of formation save that obtained from 2-*m*-tolyloxyphenyldichloroarsine, which could undergo ring-closure to give either 10-chloro-3-methylphenoxarsine (A) or 10-chloro-1-methylphenoxarsine (B).

(A.) 



(B.)

In fact (A) was the product formed, as was shown by the unambiguous synthesis:



Replacement of NH_2 by $AsO(OH)_2$ in (C) was not found possible, and the alternative synthesis described had to be adopted.

Experimental.

Preparation of Nitro-ethers.—These were all prepared by the general method of Henley (J., 1930, 1222).

2-*Nitro*-2′-*methyldiphenyl ether.* Cook (*J. Amer. Chem. Soc.*, 1901, **23**, 806) described this as a liquid. It was obtained in 80% yield, and crystallised from alcohol or light petroleum (b. p. 40—60°) in yellow hexagonal plates, m. p. 39—40°.

2-*Nitro*-3′ : 5′-*dimethyldiphenyl ether*, from symmetrical *m*-xylenol, was obtained in 64% yield. It separated from alcohol in many-faceted, pale yellow rhombohedra, m. p. 63—64° (Found : N, 5·8. $C_{14}H_{13}O_3N$ requires N, 5·8%).

2-*Nitro*-2′ : 5′-*dimethyldiphenyl ether* was obtained in 53% yield as an amber-coloured liquid, b. p. 234—235°/44 mm. (Found : N, 5·5%). 2-*Nitro*-2′ : 4′-*dimethyldiphenyl ether*, obtained in 78% yield, crystallised from alcohol in pale yellow, square plates, m. p. 61—62° (Found : N, 5·8%).

2-*Nitro*-4′-*methoxydiphenyl ether* was obtained from *p*-methoxyphenol in 80% yield, and crystallised from alcohol or from light petroleum (b. p. 40—60°) in pale yellow, hexagonal prisms, m. p. 75—76·5° (Found : N, 5·9. $C_{13}H_{11}O_4N$ requires N, 5·7%).

Preparation of Amino-ethers.—The above nitro-ethers were reduced at 100° with excess of iron filings and water in presence of a little acetic acid.

2-*Amino*-3′ : 5′-*dimethyldiphenyl ether* (yield, 77%) crystallised from alcohol in rectangular plates, m. p. 56—57° (Found : N, 6·9. $C_{14}H_{15}ON$ requires N, 6·6%). 2-*Amino*-2′ : 5′-*dimethyldiphenyl ether* (yield 83%) had b. p. 213—214°/44 mm. (Found : N, 6·9%); its hydrochloride had m. p. 178—179°. 2-*Amino*-2′ : 4′-*dimethyldiphenyl ether* (yield 80%) separated from light petroleum (b. p. 40—60°) in prisms, m. p. 64—65° (Found : N, 6·9%). 2-*Amino*-4′-*methoxydiphenyl ether* (yield 80%) had b. p. 212—213°/21 mm. (Found : N, 6·4. $C_{13}H_{13}O_2N$ requires N, 6·5%); its hydrochloride, needles from alcoholic hydrochloric acid, had m. p. 169—170°.

Preparation of Arsonic Acids.—The amino-compounds were converted into the arsonic acids by the method of Roberts and Turner (*loc. cit.*). The yield obtained varied from compound to

compound and with the temperature of mixing, so the optimum temperature is recorded in each case in parenthesis.

2-o-*Tolyloxyphenylarsonic acid* (50—60°), long prisms, m. p. 184—185°, from dilute alcohol, was obtained in 20—35% yield (Found : As, 24·4. $C_{13}H_{13}O_4As$ requires As, 24·3%); the *m*-tolyl *acid* (50—60°) (yield, 30—40%) separated from dilute alcohol in prisms, m. p. 193—194° (Found : As, 24·4%). 2-(3′ : 5′-*Dimethylphenoxy*)*phenylarsonic acid* (90°), obtained in 12% yield, separated from dilute alcohol in prisms, m. p. 178—179° (Found : As, 23·1. $C_{14}H_{15}O_4As$ requires As, 23·1%). The 2′ : 5′-dimethyl *acid* (50—60°) (yield, 13%) crystallised from dilute alcohol in needles, m. p. 177·5—178° (Found : As, 23·4%); and the 2′ : 4′-*acid* (90°) (yield, 12—16%) separated from dilute alcohol in long prisms, m. p. 184—185° (Found : As, 23·4%).

2-p-*Anisyloxyphenylarsonic acid* (50°) (yield, 11%) crystallised from dilute alcohol in octahedra, m. p. 188—189° (Found : As, 23·3. $C_{13}H_{13}O_5As$ requires As, 23·1%).

2-p-*Bromophenoxyphenylarsonic acid* (55—60°), obtained in 20% yield, separated from dilute alcohol in needles, m. p. 183—184° (Found : As, 20·8. $C_{12}H_{10}O_4BrAs$ requires As, 20·1%).

Preparation of Dichloroarsines.—The method of Roberts and Turner (*loc. cit.*) was employed. The crude dichloroarsines were purified through the oxides, which were usually obtained in a hydrated form. These were dissolved in chloroform, the solution dried over anhydrous sodium sulphate, filtered, and precipitated with ether. The dichloroarsines were prepared by warming the pure oxides with fuming hydrochloric acid. Liquid dichloroarsines were extracted with chloroform, and the extract dried and filtered. The solvent was removed either in a current of dry air or in a vacuum.

2-o-*Tolyloxyphenyldichloroarsine* formed needles, m. p. 73—74°, from light petroleum (b. p. 40—60°) (Found : Cl, 21·8. $C_{13}H_{11}OCl_2As$ requires Cl, 21·6%); the *m*-tolyl *isomeride* was an oil (Found : Cl, 21·5%); and the *p*-tolyl *compound* crystallised from light petroleum (b. p. 40—60°) in needles, m. p. 73° (Found : Cl, 21·9%).

2-(3′ : 5′-*Dimethylphenoxy*)*phenyldichloroarsine*, m. p. 71·5—73° (Found : Cl, 20·7. $C_{14}H_{13}OCl_2As$ requires Cl, 20·7%), the 2′ : 5′-*arsine*, m. p. 70—71·5° (Found : Cl, 20·9%), and the 2′ : 4′-*arsine*, m. p. 52·5—54° (Found : Cl, 20·5%), all crystallised from light petroleum (b. p. 40—60°) in prisms.

2-p-*Anisyloxyphenyldichloroarsine*, m. p. 63—64° (Found : Cl, 20·9. $C_{13}H_{11}O_2Cl_2As$ requires Cl, 20·6%), crystallised similarly.

2-p-*Bromophenoxyphenyldichloroarsine* crystallised from light petroleum (b. p. 40—60°) in rectangular prisms, m. p. 76—77° (Found : Cl, 18·4. $C_{12}H_8OCl_2BrAs$ requires Cl, 18·0%).

Preparation of Chlorophenoxarsines.—The material remaining after the experiments on rate of ring-closure was purified, all the following seven compounds being crystallised from alcohol. 10-*Choro*-4-*methylphenoxarsine* formed prisms, m. p. 90—91° (Found : Cl, 12·3. $C_{13}H_{10}OClAs$ requires Cl, 12·0%); 3-*methyl*isomeride, clusters of needles, m. p. 140—141° (Found : Cl, 12·0%); 1 : 3-*dimethyl*-compound, prisms, m. p. 138—139° (Found : Cl, 11·7. $C_{14}H_{12}OClAs$ requires Cl, 11·6%); 1 : 4-*dimethyl*-compound, prisms, m. p. 146—147° (Found : Cl, 11·4%); 2 : 4-*dimethyl*-compound, prisms, m. p. 130—131° (Found : Cl, 11·8%); 2-*methoxy*-compound, needles, m. p. 108—109° (Found : Cl, 11·3. $C_{13}H_{10}O_2ClAs$ requires Cl, 11·5%); and 10-*chloro*-2-*bromophenoxarsine*, prisms, m. p. 172—173° (Found : Cl, 9·7. $C_{12}H_7OClBrAs$ requires Cl, 9·9%).

Synthesis of 10-*Chloro*-3-*methylphenoxarsine.*—2-*Nitro*-5-*methyldiphenyl ether.* This was prepared in 50% yield from 3-chloro-4-nitrotoluene (cf. preparation from 3 : 4-dinitrotoluene and phenol; D.R.-P. 506,339).

2-*Amino*-5-*methyldiphenyl ether*, formed by stannous chloride reduction of the above compound (77% yield), was a yellow liquid, b. p. 213—214°/55 mm. (Found : N, 7·4. $C_{13}H_{13}ON$ requires N, 7·0%).

Experiments to couple the diazonium salt of this compound with sodium arsenite solution failed. The mercury diazonium salt was therefore prepared (cf. Nesmejanow, Gluschnew, Epifansky and Flegontow, *Ber.*, 1934, **67**, 130), decomposed at −70° over a period of 20 hours, and the product heated with arsenic trichloride. After purification, the resulting oil was heated for 6 hours at 200° in a stream of carbon dioxide. An alcoholic extract of the residue yielded a phenoxarsine, the m. p. of which was not depressed by that of the original ring-closure product.

Determination of Rate of Ring-closure of Aryloxyphenyldichloroarsines.—The method used was similar to that of Roberts and Turner (*loc. cit.*). In order to permit of comparison between the rates of ring-closures of different dichloroarsines, three or more of the latter were always caused to undergo cyclisation in the same heating bath. For instance, in one experiment dichloroarsines A, B, C, and D would be heated side by side, in a second, C, D, E, and F, and so on. In this way a more accurate check could be secured on the relative rates of change.

The results of a typical ring-closure experiment are as follows: k is calculated for a first-order reaction.

Ring-closure of 2-p-*tolyloxyphenyldichloroarsine* (IV) *at* 180° ± 1°.

Time, mins. (t)	60	120	180	240	300	360
Total percentage change in time t	46·4	71·0	85·3	91·6	96·1	98·0
$k \times 10^3$ (min.$^{-1}$)	10·4	10·3	10·7	10·3	10·8	10·9

Mean $k = 10{\cdot}6 \times 10^{-3}$.

Three repetitions of this experiment gave figures in agreement with those recorded, the final mean value for k being 11×10^{-3}.

In some instances cyclisation began only after a brief induction period. In such cases, $\log a/(a - x)$ plotted against t gave a straight line not passing through $t = 0$. In calculating k, the value of t corresponding with the intersection of the straight line plot with the t axis was taken as zero.

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