438. *The Formation of Phenoxyacetic Acids from Alkoxybenzenes and Diazoacetic Ester.*

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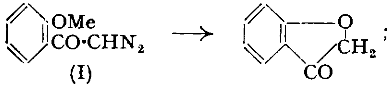
Alkoxybenzenes are partly converted with expulsion of one *O*-alkyl group into phenoxyacetic acids during Buchner-type ring-expansions with diazoacetic ester. Methylenedioxybenzene, when heated with diazoacetic ester, yields benzodioxen-2-carboxylic ester.

Recent papers from this laboratory have dealt with the conversion of alkoxybenzenes into tropolones and related compounds by ring expansion with diazoacetic ester and subsequent oxidation of the intermediate esters with bromine (Bartels-Keith, Johnson, *et al.*, *J.*, 1951, 2352; 1952, 4461). In all of these diazoacetic ester reactions, besides the required *cyclo*heptatrienecarboxylic ester, a phenoxyacetic ester was produced in yields of up to 40%, but generally 5—10%, based on the quantity of alkoxybenzene which reacted. In these reactions one of the alkyl groups of the alkoxybenzene was replaced by a carbethoxymethyl group and the possibility that such a transformation might be caused by chloroacetic ester, known to be present (up to 10%) in diazoacetic ester when prepared by Womack and Nelson's method (*Org. Syntheses*, 1944, **24**, 56) and used without distillation, was at first considered. This was disproved when similar quantities of phenoxyacetic esters were obtained from reactions with pure diazoacetic ester prepared from glycine ester in the absence of chloride ions (Skinner, *J. Amer. Chem. Soc.*, 1924, **46**, 731). Furthermore, no phenoxyacetic ester was obtained from anisole and chloroacetic ester boiling under reflux. It has been established that the carbon atom expelled in the formation of phenoxyacetic ester from anisole and diazoacetic ester is that contained in the methyl group, for a similar reaction with phenetole also gave phenoxyacetic ester together with 4-ethoxy*cyclo*hepta-1 : 3 : 5-trienecarboxylic ester (Bartels-Keith, Johnson, and Langemann, *J.*, 1952, 4461). Only very small quantities of phenolic compounds were obtained from these reactions; *e.g.*, a little *p*-hydroxyphenoxyacetic ester was isolated in the experiment with quinol dimethyl ether, and it is very unlikely that the free phenols are intermediates.

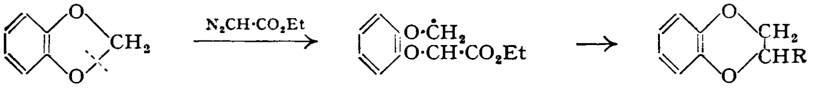
The fission of alkyl aryl ethers with diazoacetic ester is related formally to the intramolecular cyclisation of *o*-anisoyldiazomethane (I) to coumaranone and similar reactions (Pfeiffer and Enders, *Chem. Ber.*, 1951, **84**, 247; Marshall and Walker, *J.*, 1952, 467; Bose and Yates, *J. Amer. Chem. Soc.*, 1952, **74**, 4703). The cyclisation of (I) was brought about by the action of dilute hydrochloric acid at room temperature and operates by an ionic mechanism. On the other hand, the diazoacetic ester condensations described in the present paper were carried out at 150° in the absence of solvent and a free-radical mechanism is more probable, especially as fumaric ester is frequently isolated from the reaction mixture, and phenoxyacetic ester was also produced from anisole and diazoacetic ester after irradiation with ultra-violet light. In this connection it is of interest that Seth and Deshapande (*J. Indian Chem. Soc.*, 1950, **27**, 429) have obtained a compound, not identified, by heating (I) in the absence of solvent or acid, and from the physical constants given for their product and its derivatives it is almost certainly coumaranone. There is therefore fairly good evidence that the two different mechanisms, ionic and free-radical, may operate in these condensations, and lead to the same products.



(I)

$$\text{PhOMe} \xrightarrow{N_2CH{\cdot}CO_2Et} \text{PhO}{\cdot}CH_2{\cdot}CO_2Et$$

In attempts to determine the fate of the expelled alkyl radical the reaction of diazoacetic ester with the cyclic ethers chroman and methylenedioxybenzene has been examined and the crude ester mixture fractionated and converted into the corresponding acids as before. In the case of methylenedioxybenzene, the main acidic product was identified as benzodioxen-2-carboxylic acid (II; $R = CO_2H$) by comparison with an authentic specimen prepared by the alkaline condensation of catechol with αβ-dibromopropionic ester. Reduction of the acid (II; $R = CO_2H$) with lithium aluminium hydride gave the corresponding alcohol (II; $R = CH_2{\cdot}OH$) which has been obtained previously (J. R. Geigy, S.A., U.S.P. 2,366,102; *Chem. Abs.*, 1946, **40**, 2271). The gift of a specimen of this compound from J. R. Geigy, S.A., is gratefully acknowledged. The conversion of methylenedioxybenzene into (II; $R = CO_2Et$) is quite analogous to the production of phenoxyacetic ester from anisole. One of the oxygen–alkyl carbon bonds is split as the $CH{\cdot}CO_2Et$ diradical attacks the oxygen, and the resulting diradical (III) forms the dioxan ring by intramolecular addition :



(II)

On the other hand, the main crystalline acid isolated from the reaction of chroman with diazoacetic ester was a chromano*cyclo*heptatrienecarboxylic acid, the exact structure of which was not determined. The steric factors for the expansion of the six-membered heterocyclic ring are not so favourable in this case and the alternative Buchner-type ring expansion of the aromatic ring is therefore more prominent.

During this work a number of substituted phenoxyacetic acids and their derivatives were prepared and these are recorded in the Experimental section. The phenoxyacetic acids, either in dioxan solution or as Nujol mulls, showed two carbonyl bands in their infra-red spectra (Table), a feature not exhibited in the spectra of the corresponding esters. The same phenomenon was observed with methoxyacetic acid, either as a liquid film or in dioxan solution, and it seems to be a characteristic of the alkoxy- and aryloxy-acetic acids. Flett (*J.*, 1951, 962) has recorded that the infra-red spectrum of glycollic acid also shows two bands in the carbonyl region of its infra-red spectrum.

*Infra-red spectra of alkoxyacetic and aryloxyacetic acids and derivatives**
(" carbonyl region " only).

Substituted acetic acid	Wave nos. of " carbonyl region " bands	
Methoxy- (liquid film)	1755	1725
Methoxy- (dioxan)	1761	1740
Phenoxy- (cp. Flett, *loc. cit.*)	1740	1705
o-Methoxyphenoxy-	1745	1715
m-Methoxyphenoxy-	1755	1720
m-Methoxyphenoxy- (dioxan)	1768	1742
p-Methoxyphenoxy-	1738	1710
2 : 5-Dibromo-4-methoxyphenoxy-	1760	1730
2 : 4-Dimethoxyphenoxy-, m. p. 108°	1750	1718
2 : 4-Dimethoxyphenoxy-, m. p. 121°	1750	1712
2 : 5-Dimethoxyphenoxy-	1752	1718
o-Ethoxyphenoxy-	1726	(?)1685
2 : 6-Dimethylphenoxy-	1736	(?)1710
p-Hydroxyphenoxy-	1745	1718
p-$C_6H_4(O{\cdot}CH_2{\cdot}CO_2H)_2$	1740	1710

* Determined as Nujol mulls except where otherwise stated.

EXPERIMENTAL

Diazoacetic ester and the alkoxybenzenes were condensed at 150° for 5—6 hr. and the products fractionated (Bartels-Keith, Johnson, *et al.*, *locc. cit.*). The mixed ester fractions so obtained were hydrolysed with methanolic potassium hydroxide, and the potassium phenoxyacetates which separated from the cooled reaction products were removed, washed, and converted into the corresponding acids.

Phenoxyacetic Acids from Alkoxybenzenes.—The following examples have been studied. The yields of the phenoxyacetic acids varied widely in different experiments and were considerably affected by small changes in the experimental conditions.

(i) Anisole and phenetole gave phenoxyacetic acid (4—7 and 20% respectively).

(ii) *o*-, *m*-, and *p*-Dimethoxybenzenes gave *o*-, m. p. 120—121° (up to 38%), *m*-, m. p. 116°

(up to 14%), and *p*-, m. p. 112° (up to 40%), methoxyphenoxyacetic acid respectively, which were identified by comparisons with authentic specimens.

The mixed ester fraction (2 g.) from the quinol dimethyl ether experiment was heated at 100° with 2N-hydrochloric acid (40 c.c.) and acetic acid (10 c.c.) for 5 hr. The mixture was diluted with water, and the product extracted into ether and separated into acidic, phenolic, and neutral fractions. From the acidic fraction there was obtained a little *p*-methoxyphenoxyacetic acid together with two unidentified acids, one (5 mg.) forming colourless needles, m. p. 48°, from *cyclo*hexane, and the other being a yellow phenolic oil. The main phenolic fraction gave ethyl *p*-hydroxyphenoxyacetate as colourless crystals, m. p. 120° (from dilute ethanol) not depressed on admixture with an authentic specimen (Sobotka and Austin, *J. Amer. Chem. Soc.*, 1952, **74**, 3813), and an unidentified colourless *substance*, b. p. 140° (bath-temp.)/0·1 mm., m. p. 0° (Found: C, 61·2; H, 6·1. $C_{10}H_{12}O_4$ requires C, 61·2; H, 6·2%). Treatment of the neutral oil (ethyl *p*-methoxyphenoxyacetate) with bromine gave colourless needles of *ethyl* 2 : 5-*dibromo*-4-*methoxyphenoxyacetate*, m. p. 76° (from methanol) (Found: C, 36·2; H, 3·3. $C_{11}H_{12}O_4Br_2$ requires C, 36·0; H, 3·3%). This ester was occasionally obtained in a second *form*, m. p. 95° [Found: C, 35·7; H, 3·5; *O*-Me, 16·7; Br, 44·3%; *M* (Rast), 370. $C_{11}H_{12}O_4Br_2$ requires C, 36·0; H, 3·3; 2*O*-Me, 16·85; Br, 43·8%; *M*, 368). The ultra-violet absorption spectra of these forms were identical (max. at 297 and 229 mμ; log ε 3·70 and 4·07 respectively, in ethanol), and the latter form was largely converted into the former by heating a methanolic solution under reflux. Both forms on hydrolysis gave 2 : 5-*dibromo*-4-*methoxyphenoxyacetic acid*, as prisms, m. p. 181° (from acetic acid) (Found: C, 32·1; H, 2·6. $C_9H_8O_4Br_2$ requires C, 31·8; H, 2·35%). The ultra-violet absorption spectrum of this acid in ethanolic solution showed a maximum at 298 mμ (log ε 3·70) and an inflexion at 223—229 mμ (log ε 4·13).

(iii) 1 : 2 : 4-Trimethoxybenzene gave 2 : 4-*dimethoxyphenoxyacetic acid*, m. p. 106—108°, as colourless prisms (sublimation) (Found: C, 56·7; H, 5·7. $C_{10}H_{12}O_5$ requires C, 56·6; H, 5·7%). This acid also existed in two forms, the other having m. p. 120° (see below). The lower-melting form was converted into the higher-melting after being heated at 130° for 10 min. *Ethyl* 2 : 4-*dimethoxyphenoxyacetate* had m. p. 49—50° (from aqueous ethanol) (Found: C, 60·2; H, 6·6. $C_{12}H_{16}O_5$ requires C, 60·0; H, 6·7%).

(iv) Methylenedioxybenzene gave a crude ester mixture, the main fraction of which was a yellow liquid, b. p. 101—110°/0·2 mm. This fraction (1·8 g.) was hydrolysed by adding an ice-cold solution of potassium hydroxide (1·1 g.) in methanol (10 c.c.) and subsequently heating the whole on the steam-bath for 1 hr. No potassium salt was precipitated and the solution was acidified with 10N-hydrochloric acid (1·7 c.c.) and diluted with water (30 c.c.). No acid was precipitated and the solution was extracted with ether and the ethereal extract after drying and removal of solvent yielded a brown resin which slowly crystallised. Repeated extraction of this product with hot *cyclo*hexane gave a pale yellow powder (369 mg.), and a further quantity (34 mg.) was obtained by sublimation of the residue *in vacuo*. Crystallisation from *cyclo*hexane–ether gave *benzodioxen-2-carboxylic acid* as colourless short needles, m. p. 116—117° (Found: C, 60·0; H, 4·5. $C_9H_8O_4$ requires C, 60·0; H, 4·5%). The ultra-violet absorption spectrum of a solution in methanol showed max. at 282 and 276 mμ (log ε 3·33 and 3·38 respectively) and min. at 280 and 243 mμ (log ε 3·31 and 1·54 respectively). A solution of the acid decolorised bromine in chloroform and potassium permanganate in acetone only very slowly. It gave no colour with concentrated sulphuric acid, and the colour test for the methylenedioxy-group with gallic acid and sulphuric acid was negative.

(v) Chroman (de Benneville and Connor, *J. Amer. Chem. Soc.*, 1940, **62**, 283) gave a chromano*cyclo*heptatrienecarboxylic acid (16%), m. p. 165—166° (from *cyclo*hexane) (Found: C, 68·7; H, 6·2. $C_{11}H_{12}O_3$ requires C, 68·7; H, 6·3%). The ultra-violet absorption spectrum of an ethanolic solution showed max. at 325 and 227 mμ (log ε 4·03 and 4·07 respectively). The acid rapidly decolorised a solution of bromine in chloroform as well as of potassium permanganate in acetone. A yellow colour was obtained with concentrated sulphuric acid.

Reaction of Anisole and Diazoacetic Ester under Ultra-violet Irradiation.—Anisole (216 g.) was mixed with diazoacetic ester (25 c.c.) and irradiated with ultra-violet light for 3 weeks. Excess of the reactants was removed from the brown mixture under reduced pressure (steam-bath), and the dark brown residue fractionated into the following: (i) b. p. 79—87°/0·01 mm. (4·4 g.), a light yellow oil giving a dark red colour with concentrated sulphuric acid; (ii) b. p. 93—120°/0·01 mm. (1·1 g.), a dark yellow oil; and (iii) residue (5·2 g.), a brown tar. Fraction (i) (1 g.) was saponified with an ice-cooled solution of potassium hydroxide (0·3 g.) in methanol (5 c.c.), and the potassium salt which precipitated was separated and dried (284 mg.). Acidification gave phenoxyacetic acid (167 mg.), m. p. 99°.

Benzodioxen-2-carboxylic Acid.—A solution of potassium hydroxide (36 g.) in water (130 c.c.) was heated with catechol (22 g.) and ethyl αβ-dibromopropionate (50 g.) in an autoclave at 145° for 1½ hr. After cooling, the dark mixture was acidified with concentrated hydrochloric acid and extracted with ether (2 × 500 c.c.). The combined ethereal solutions were extracted with saturated aqueous sodium hydrogen carbonate (3 × 150 c.c.), and the aqueous extracts again acidified and extracted with ether (2 × 200 c.c.). The solvent was removed from the dried ethereal extracts, and the dark brown solid residue crystallised from *cyclo*hexane–ether to give, after clarification with charcoal, colourless prisms of benzodioxen-2-carboxylic acid (24·1 g., 67%), m. p. 116—117° not depressed on admixture with the product obtained from methylenedioxybenzene (Found, on a sample sublimed at 0·05 mm.: C, 60·0; H, 4·7. Calc. for $C_9H_8O_4$: C, 60·0; H, 4·5%). The infra-red spectrum (Nujol mull) was identical with the product prepared from methylenedioxybenzene: max. at 1730(s), 1600, 1497(s), 1420, 1364, 1333, 1316, 1290, 1252(s), 1224(s), 1198(s), 1156, 1127(s), 1099(s), 1064(s), 1013, 939, 923, 893, 853, 833, 806, 757(s), 738, 714, and 692 cm.$^{-1}$. The ultra-violet absorption in 95% ethanol showed maxima at 282 and 276 mμ (log ε 3·33 and 3·38 respectively).

2-Hydroxymethylbenzodioxen.—Benzodioxen-2-carboxylic acid (1·01 g.) in dry ether (20 c.c.) was added with stirring to a cooled suspension of lithium aluminium hydride (360 mg.) in dry ether (30 c.c.). The mixture was heated under reflux for 2½ hr., cooled (ice), and decomposed with wet ether followed by water, and finally 4N-sulphuric acid. The ethereal layer was separated and the aqueous layer further extracted with ether (2 × 25 c.c.), and the combined ethereal solutions were washed with aqueous sodium hydrogen carbonate (2 × 15 c.c.), dried, and freed from solvent. The residue crystallised from ether–light petroleum (b. p. 60—80°) as colourless needles (817 mg., 88%), m. p. 85—87° raised to 89—90° after sublimation at 0·05 mm. and not depressed with an authentic specimen (J. R. Geigy, S.A., *loc. cit.*) (Found: C, 65·0; H, 6·3. Calc. for $C_9H_{10}O_3$: C, 65·05; H, 6·1%). The infra-red spectrum (Nujol mull) showed maxima at 3175(s), 2041, 1923, 1887, 1770, 1592(s), 1497(s), 1395, 1346, 1324, 1304, 1269(s), 1234, 1205(s), 1178, 1148, 1136(s), 1101(s), 1075(s), 1039(s), 1015, 961, 942(s), 925, 919, 893, 844(s), 761, 749(s), and 678 cm.$^{-1}$.

2 : 4-*Dimethoxyphenoxyacetic Acid.*—The dimethyl ether of resacetophenone (*Org. Synth.*, 1941, **21**, 103) was treated with peracetic acid, to give 2 : 4-dimethoxyphenol, b. p. 140°/15 mm., and the sodium salt of the latter treated with chloroacetic acid to give 2 : 4-*dimethoxyphenoxyacetic acid* as prisms, m. p. 120—121° (from aqueous acetone) (Found: C, 56·4; H, 5·8. $C_{10}H_{12}O_5$ requires C, 56·6; H, 5·7%).

2 : 5-*Dimethoxyphenoxyacetic Acid.*—Prepared as was the preceding acid from quinacetophenone (*Org. Synth.*, 1948, **28**, 42), the *acid* formed needles, m. p. 128—129° (Found: C, 56·3; H, 5·75%).

o-*Ethoxyphenoxyacetic acid.*—*o*-Hydroxyphenoxyacetic acid was ethylated with diazoethane, and the resulting ester hydrolysed with sodium carbonate solution, to give o-*ethoxyphenoxyacetic acid* as needles, m. p. 70° (from aqueous acetone) (Found, in a sample dried overnight at 40°/10 mm.: C, 56·4; H, 6·6. $C_{10}H_{12}O_4,H_2O$ requires C, 56·1; H, 6·6%). The water of crystallisation was only partly removed after sublimation *in vacuo*.

Bromination of o-*Methoxyphenoxyacetic Acid.*—The acid, m. p. 122° (1 mol.), heated with bromine (1 mol.) in chloroform, gave *ethyl 5-bromo-2-methoxyphenoxyacetate* as a colourless oil, b. p. 90° (bath-temp.)/0·01 mm. (Found: C, 45·4; H, 4·5. $C_{11}H_{13}O_4Br$ requires C, 45·6; H, 4·5%). The ester is formed by esterification of the acid with the small quantity of ethanol normally present as a stabiliser in chloroform. Alkaline hydrolysis of the ester gave the corresponding *acid*, m. p. 134°, as colourless needles after sublimation (Found: C, 41·7; H, 3·7. $C_9H_9O_4Br$ requires C, 41·4; H, 3·5%).

When *o*-methoxyphenoxyacetic acid was treated with excess of bromine in chloroform, ethyl 3(?) : 5-*dibromo-2-methoxyphenoxyacetate* was obtained as colourless prisms, m. p. 94—95° (Found: C, 36·6; H, 3·8. $C_{11}H_{12}O_4Br_2$ requires C, 36·9; H, 3·4%).

Bromination of p-*Methoxyphenoxyacetic Acid.*—Ethyl *p*-methoxyphenoxyacetate (2 g.) was heated with bromine (0·58 c.c.) in chloroform (30 c.c.) for 15 min. under reflux, and the product cooled and extracted with sodium hydrogen carbonate solution. The neutral residue, after removal of the solvent, crystallised in large prisms of ethyl 3(?)-*bromo-4-methoxyphenoxyacetate*, m. p. 44° (from methanol) (Found: C, 45·9; H, 4·9. $C_{11}H_{13}O_4Br$ requires C, 45·7; H, 4·5%). The ester was hydrolysed with 2N-sodium carbonate to the corresponding acid, m. p. 139—140°, which formed colourless needles (from aqueous acetone). Further bromination of ethyl 3(?)-bromo-4-methoxyphenoxyacetate gave ethyl 2 : 5-dibromo-4-methoxyphenoxyacetate, m. p. 76°, identical with that described above. Hydrolysis of the dibromo-ester as before gave the corresponding acid, m. p. 181°, which on decarboxylation with soda-lime gave 2 : 5-dibromo-1 : 4-dimethoxybenzene, m. p. 144° alone and mixed with an authentic specimen obtained by bromination of quinol dimethyl ether.

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