

328. Reactivity of the ω -Halogen Atom in *p*-Alkoxybenzyl Halides : Preparation of Phenylacetic Acids.

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p-Alkoxybenzyl alcohols (obtained from the aldehydes by the Cannizzaro reaction) give with halogen acids the corresponding chlorides and bromides, and these, with potassium cyanide, yield *p*-alkoxyphenylacetone nitriles and thence *p*-alkoxyphenylacetic acids. The ω -halogen atom in the *p*-alkoxybenzyl halides readily reacts with alcohols.

IN continuation of work on the reactivity of the mobile β -halogen atom in phenyl $\alpha\beta$ -dihalogeno- β -*p*-alkoxyphenylethyl ketones (Nadkarni *et al.*, J., 1937, 1798), a study has been made of the activating effect of the alkoxy-group in *p*-alkoxybenzyl halides; Lapworth and Shoemith (J., 1922, 121, 1391) had shown that *p*-methoxybenzyl bromide is very readily hydrolysed.

6-Chloro- and 6-bromo-3 : 4-methylenedioxybenzyl and 3-chloro- and 3-bromo-4-methoxybenzyl alcohols were made from the corresponding aldehydes (the *anils* were prepared for the purpose of characterisation) by the Cannizzaro reaction (for an improved method, see Ahmad, Narang, and Ray, *J. Indian Chem. Soc.*, 1938, 15, 157), and converted into the corresponding *chlorides* and *bromides* by treatment in benzene solution with hydrogen chloride or directly with concentrated hydrobromic acid. With potassium iodide in aqueous acetone solution, these halides gave the corresponding *iodides*, which gradually decomposed with liberation of iodine on exposure to air. With alcoholic potassium cyanide, the chlorides and bromides gave the corresponding *halogenoalkoxyphenylacetone nitriles*, which were readily hydrolysed to the corresponding *acids*; this method of preparing these acids is simpler than that hitherto used, *viz.*, from the arylaldehyde through the azlactone (cf., *e.g.*, Angeli and Rimini, *Gazzetta*, 1895, 25, ii, 206; Girardet, *Helv. Chim. Acta*, 1931, 14, 514; Stevens, J., 1935, 667; Kondo and Uyeo, *J. Pharm. Soc. Japan*, 1933, 53, 557). The phenylacetic acids are important, as they are necessary in the Bischler-Napieralski synthesis of *isoquinolines*.

The mobility of the side-chain halogen atom is shown by the fact that the 3-halogeno-4-methoxybenzyl halides gave ethers on boiling with methyl and ethyl alcohols. The alkoxy-group so introduced could be replaced by halogen on treatment with hydrochloric or hydrobromic acid.* Kobayashi (*Sci. Papers Inst. Phys. Chem. Res. Tokyo*, 1927, 6,

* For a discussion of the application of the electronic theory to the reactions of *p*-alkoxybenzyl halides, see Watson ("Modern Theories of Organic Chemistry," 1937, 52, 67).

149) obtained 3 : 4-methylenedioxybenzyl ethyl ether as a by-product when preparing piperonylacetonitrile from 3 : 4-methylenedioxybenzyl chloride by treatment with alcoholic potassium cyanide. The alcohol evidently reacted directly with the halide. On the other hand, when 3 : 4-methylenedioxybenzyl bromide was heated with methyl or ethyl alcohol, 2 : 3 : 6 : 7-bismethylenedioxy-9 : 10-dihydroanthracene was formed; this compound has previously been prepared by Ewins (J., 1909, **95**, 1482) by autopolymerisation of 3 : 4-methylenedioxybenzyl chloride, and also by the action of phosphorus pentachloride on 3 : 4-methylenedioxybenzyl alcohol in chloroform solution. Its formation from the 3 : 4-methylenedioxybenzyl halide is apparently catalysed by acids; by heating 3 : 4-methylenedioxybenzyl bromide with methyl alcohol in presence of sodium carbonate, 3 : 4-methylenedioxybenzyl methyl ether was readily obtained; the potassium cyanide used by Kobayashi evidently played the same rôle as sodium carbonate in neutralising mineral acid.

The 6-halogeno-3 : 4-methylenedioxybenzyl halides reacted with alcohols without formation of dihydroanthracene derivatives, but the oils obtained, though they gave 3 : 4-methylenedioxybenzyl halides on treatment with halogen acids, always contained more halogen than the expected ethers. 6-Nitro-3 : 4-methylenedioxybenzyl chloride did not react with alcohols.

6-Halogeno-3 : 4-methylenedioxybenzyl chloride and bromide with phosphorus pentachloride gave 6-halogeno-3 : 4-dichloromethylenedioxybenzyl chloride (cf. Ewins, *loc. cit.*); it will be noted that bromine in the side chain was also replaced by chlorine. These compounds are unstable, and it was not possible to obtain accurate halogen analyses for them; on treatment with cold formic acid 6-halogeno-3 : 4-carbonyldioxybenzyl chlorides were formed.

When bromine (1 mol.) is added to 3 : 4-methylenedioxybenzyl alcohol or methyl ether, 6-bromo-3 : 4-methylenedioxybenzyl bromide is obtained; the hydrogen bromide formed, when bromine enters the nucleus, reacts with the hydroxy- or alkoxy-group.

EXPERIMENTAL.

[Analysis of side-chain halogen was carried out by the method of Gavankar, Heble, and Wheeler, *J. Univ. Bombay*, 1937, **6**, (ii), 112.]

Alkoxybenzaldehydes and Corresponding Anils.—The following aldehydes were prepared by the methods indicated: 6-chloropiperonal (Orr, Robinson, and Williams, J., 1917, **111**, 948); 6-bromopiperonal (Oelker, *Ber.*, 1891, **24**, 2592; bromination was carried out in glacial acetic acid instead of carbon disulphide, and the solid product recovered by dilution with water after removal of hydrogen bromide under reduced pressure); 3-chloro-*p*-anisaldehyde (Nadkarni *et al.*, *loc. cit.*); 3-bromo-*p*-anisaldehyde (Brady and Manjunath, J., 1924, **125**, 1063). The following anils were readily prepared by heating the aldehyde with aniline at 100°, washing the product with alcohol to remove the excess of aniline, and crystallising it from alcohol. 6-Chloropiperonylideneaniline (Found: Cl, 13.9. $C_{14}H_{10}O_2NCl$ requires Cl, 13.7%), m. p. 112°; 6-bromopiperonylideneaniline (Found: Br, 26.5. $C_{14}H_{10}O_2NBr$ requires Br, 26.3%), m. p. 131—132°; 3-chloro-4-methoxybenzylideneaniline (Found: Cl, 14.2. $C_{14}H_{12}ONCl$ requires Cl, 14.4%), m. p. 85°; 3-bromo-4-methoxybenzylideneaniline (Found: Br, 27.5. $C_{14}H_{12}ONBr$ requires Br, 27.6%), m. p. 96—97°.

Alkoxybenzyl Alcohols.—6-Chloropiperonal (25 g.) was treated at 50° with aqueous sodium hydroxide (50%; 100 g.), alcohol (5 c.c.) added, the mixture was kept overnight, diluted with water, and extracted with ether. The extract was washed with sodium hydrogen sulphite solution and dried over calcium chloride; on evaporation it gave 6-chloro-3 : 4-methylenedioxybenzyl alcohol (10 g.), which separated from light petroleum in colourless needles, m. p. 73—74° (Found: Cl, 19.0. $C_8H_7O_2Cl$ requires Cl, 19.0%). The following were similarly prepared, the solids being crystallised from light petroleum: 6-Bromo-3 : 4-methylenedioxybenzyl alcohol (Found: Br, 35.0. $C_8H_7O_2Br$ requires Br, 34.6%), m. p. 90°; 3-chloro-4-methoxybenzyl alcohol (Found: Cl, 20.3. $C_8H_9O_2Cl$ requires Cl, 20.5%), b. p. 178—180°/10 mm.; 3-bromo-4-methoxybenzyl alcohol (Found: Br, 36.8. $C_8H_9O_2Br$ requires Br, 36.8%), m. p. 63—64°.

Alkoxybenzyl Chlorides and Bromides.—6-Chloro-3 : 4-methylenedioxybenzyl chloride (14 g.) was obtained by evaporation of a solution of 6-chloro-3 : 4-methylenedioxybenzyl alcohol (15 g.) in benzene (75 c.c.), which had been saturated with dry hydrogen chloride at 0°; after

separation from the water formed, it crystallised from light petroleum; m. p. 65° (Found: total Cl, 34.8; side-chain Cl, 17.1. $C_8H_6O_2Cl_2$ requires total Cl, 34.6; side-chain Cl, 17.3%). 6-Chloro-3:4-methylenedioxybenzyl bromide (10 g.), obtained by shaking a mixture of 6-chloro-3:4-methylenedioxybenzyl alcohol (10 g.) and hydrobromic acid (*d* 1.69; 50 g.), separated from light petroleum in crystals, m. p. 75—76° (Found: total halogen, 46.0; side-chain halogen, 31.4. $C_8H_6O_2ClBr$ requires total halogen 46.3; side-chain halogen, 32.0%). The following were similarly prepared, and, if solid, crystallised from light petroleum. 6-Bromo-3:4-methylenedioxybenzyl chloride (Found: halogen, 46.0. $C_8H_6O_2ClBr$ requires halogen, 46.3%), m. p. 64—65°; 6-bromo-3:4-methylenedioxybenzyl bromide (Found: total Br, 54.7; side-chain Br, 27.4. $C_8H_6O_2Br_2$ requires total Br, 54.4; side-chain Br, 27.2%), m. p. 94°; 3-chloro-4-methoxybenzyl chloride (Found: Cl, 37.0. $C_8H_8OCl_2$ requires Cl, 37.2%), b. p. 145—147°/6 mm.; 3-chloro-4-methoxybenzyl bromide (Found: total halogen, 48.9; side-chain halogen, 33.9. C_8H_8OClBr requires total halogen, 49.0; side-chain halogen, 34.0%), m. p. 52—53°; 3-bromo-4-methoxybenzyl chloride (Found: total halogen, 49.0; side-chain halogen, 15.0. C_8H_8OClBr requires total halogen, 49.0; side-chain halogen, 15.1%), m. p. 51—52°; 3-bromo-4-methoxybenzyl bromide (Found: total Br, 56.7; side-chain Br, 28.6. $C_8H_8OBr_2$ requires total Br, 57.1; side-chain Br, 28.6%), m. p. 61—62°.

Alkoxybenzyl Iodides.—6-Chloro-3:4-methylenedioxybenzyl iodide (1.6 g.), obtained by diluting a mixture of 6-chloro-3:4-methylenedioxybenzyl chloride (2 g.), potassium iodide (1.4 g.), water (3 c.c.), and acetone (20 c.c.), which had been heated under reflux at 100° for 1½ hours, separated from light petroleum in yellowish needles, m. p. 95—96° (Found: halogen, 55.2. $C_8H_6O_2ClI$ requires halogen, 54.7%). The following compounds, also yellow, were similarly prepared and crystallised. 6-Bromo-3:4-methylenedioxybenzyl iodide (Found: halogen, 61.1. $C_8H_6O_2BrI$ requires halogen, 60.7%), m. p. 90—91°; 3-chloro-4-methoxybenzyl iodide (Found: halogen, 57.5. C_8H_8OClI requires halogen, 57.5%), m. p. 61—62°; 3-bromo-4-methoxybenzyl iodide (Found: halogen, 63.7. C_8H_8OBrI requires halogen, 63.3%), m. p. 64—65°.

Alkoxyphenylacetoneitriles.—6-Chloropiperonylacetoneitrile, which separated as an oil (9.5 g.) on dilution of a mixture of 6-chloro-3:4-methylenedioxybenzyl chloride (16 g.), potassium cyanide (8 g.), and alcohol (100 c.c.), which had been shaken for 24 hours, was extracted with ether and distilled (b. p. 190°/15 mm.). It separated from dilute alcohol in crystals, m. p. 70—71° (Found: C, 55.0; H, 2.9; N, 7.1. $C_9H_8O_2NCl$ requires C, 55.2; H, 3.1; N, 7.2%). 6-Bromopiperonylacetoneitrile (Found: N, 5.9. Calc. for $C_9H_8O_2NBr$: N, 5.8%), m. p. 71—72° (cf. Stevens, *loc. cit.*), 3-chloro-*p*-anisylacetoneitrile (Found: Cl, 19.4. C_9H_8ONCl requires Cl, 19.5%), m. p. 54—55°, and 3-bromo-*p*-anisylacetoneitrile (Found: Br, 35.9. C_9H_8ONBr requires Br, 35.4%), m. p. 56—57°, were similarly prepared; distillation was, however, not necessary in order to obtain the crude product in a solid form.

Alkoxyphenylacetic Acids.—6-Chloropiperonylacetic acid, which was obtained by acidifying with dilute hydrochloric acid a mixture of 6-chloropiperonylacetoneitrile (7 g.), sodium hydroxide (2.5 g.) in water (40 c.c.), and alcohol (15 c.c.) which had been heated under reflux at 100° for 8 hours, separated from alcohol in white needles (6 g.), m. p. 174—175° (Found: Cl, 16.7. $C_9H_7O_4Cl$ requires Cl, 16.6%). 6-Bromopiperonylacetic acid, m. p. 190° (cf. Angeli and Rimini; Girardet, *loc. cit.*), 3-chloro-*p*-anisylacetic acid (Found: Cl, 17.5. $C_9H_8O_3Cl$ requires Cl, 17.7%), m. p. 95—96°, and 3-bromo-*p*-anisylacetic acid (Found: Br, 32.9. Calc. for $C_9H_8O_3Br$: Br, 32.7%), m. p. 114—115° (cf. Kondo and Uyeo, *loc. cit.*), were similarly prepared from the corresponding nitriles.

Alkoxyphenylacetic Esters.—Methyl 6-chloropiperonylacetate, prepared by evaporating a solution of the acid (2 g.) in methyl alcohol (20 c.c.) containing sulphuric acid (0.5 c.c.), which had been heated under reflux at 100° for 6 hours, separated from light petroleum in needles, m. p. 69—70° (Found: Cl, 15.7. $C_{10}H_9O_4Cl$ requires Cl, 15.5%). The ethyl ester (Found: Cl, 14.8. $C_{11}H_{11}O_4Cl$ requires Cl, 14.6%), m. p. 60—61°, and ethyl 6-bromopiperonylacetate (Found: Br, 27.8. $C_{11}H_{11}O_4Br$ requires Br, 27.9%), m. p. 69—70°, were similarly prepared.

Alkoxybenzyl Ethers.—3-Chloro-4-methoxybenzyl methyl ether (1.8 g.), obtained by diluting a mixture of 3-chloro-4-methoxybenzyl chloride (2.5 g.) and methyl alcohol (25 c.c.), which had been heated under reflux at 100° for 2 hours, had b. p. 135—140°/5 mm. (Found: Cl, 19.0. $C_9H_{11}O_2Cl$ requires Cl, 19.0%). The ethyl ether (Found: Cl, 18.0. $C_{10}H_{13}O_2Cl$ requires Cl, 17.7%), b. p. 150—155°/10 mm., and 3-bromo-4-methoxybenzyl ether (Found: Br, 33.1. $C_{10}H_{13}O_2Br$ requires Br, 32.7%), b. p. 155—160°/10 mm., were similarly prepared. These ethers regenerated the corresponding alkoxybenzyl halides on treatment with dry hydrogen chloride in benzene solution, or directly with concentrated hydrobromic acid (*d* 1.69).

2:3:6:7-Bismethylenedioxy-9:10-dihydroanthracene (3 g.) was obtained by heating

3:4-methylenedioxybenzyl bromide (6 g.) with methyl or ethyl alcohol (60 c.c.) for 6 hours; it crystallised from nitrobenzene in white needles, m. p. above 360° (Found: C, 71.4; H, 4.4. Calc. for $C_{16}H_{12}O_4$: C, 71.6; H, 4.5%). 3:4-Methylenedioxybenzyl methyl ether separated as an oil (6.6 g.; b. p. $120^{\circ}/10$ mm.) from a mixture of 3:4-methylenedioxybenzyl bromide (10 g.), sodium carbonate (2 g.), and methyl alcohol (50 c.c.), which had been heated under reflux at 100° for $1\frac{1}{2}$ hours and diluted with water (Found: C, 65.1; H, 5.9. $C_9H_{10}O_3$ requires C, 65.0; H, 6.0%).

Carbonyldioxybenzyl Halides.—6-Chloro-3:4-dichloromethylenedioxybenzyl chloride (5 g., b. p. 150 — $154^{\circ}/10$ mm.) passed over on distillation under reduced pressure of a mixture of phosphorous pentachloride (12 g.) and 6-chloro-3:4-methylenedioxybenzyl chloride (6 g.) which had been heated at 120° (calcium chloride guard tube) for 4 hours (Found: Cl, 50.0. $C_8H_4O_2Cl_4$ requires Cl, 51.8%). Addition after 5 mins. of cold water to its solution in formic acid precipitated 6-chloro-3:4-carbonyldioxybenzyl chloride (Found: total Cl, 32.6; side-chain Cl, 15.8. $C_8H_4O_3Cl_2$ requires total Cl, 32.4; side-chain Cl, 16.2%), which separated from light petroleum in crystals, m. p. 64° . 6-Bromo-3:4-dichloromethylenedioxybenzyl chloride (Found: halogen, 57.4. $C_8H_4O_2Cl_2Br$ requires halogen, 58.5%), b. p. 155 — $157^{\circ}/10$ mm., and 6-bromo-3:4-carbonyldioxybenzyl chloride (Found: halogen, 43.7. $C_8H_4O_3ClBr$ requires halogen, 43.8%), m. p. after crystallisation from light petroleum, 80 — 81° , were similarly prepared from 6-bromo-3:4-methylenedioxybenzyl chloride or bromide. Satisfactory analyses could not be obtained for the dichloromethylene compounds owing to their instability (cf. Ewins, *loc. cit.*).

Our thanks are due to Dr. J. N. Ray and Dr. R. C. Shah for valuable advice.

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[Received, August 10th, 1938.]