CCXCVII.—*The Action of Phosphorus Pentabromide on the Isomeric β-Methoxyphenylethyl Alcohols.*

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DURING attempts to prepare the isomeric β-methoxyphenylethyl bromides by the method which served for the corresponding methyl derivatives (Shoesmith and Connor, this vol., p. 1768), it has been discovered that when the phosphorus pentabromide reacts with the isomeric β-methoxyphenylethyl alcohols, the nuclear directing power of the methoxyl group is so great that it causes the formation of nuclear-brominated derivatives of the expected β-methoxyphenylethyl bromides. Thus the only compounds isolated in a pure state are β-5-*bromo*-2-*methoxyphenylethyl bromide* from the ortho-alcohol, β-6-*bromo*-3-*methoxyphenylethyl bromide* from the meta-, and β-3-*bromo*-4-*methoxyphenylethyl bromide* from the para-alcohol. The orientation of the disubstituted β-phenylethyl bromides has been proved in each case by oxidation to the corresponding known bromomethoxybenzoic acid.

Whilst carrying out preliminary experiments on the most satisfactory methods for obtaining substituted β-phenylethyl alcohols, the authors found that β-phenylethylamine in aqueous hydrochloric acid yields with nitrous acid an appreciable quantity of β-phenylethyl chloride in sharp contrast to the production of pure alcohols from the isomeric tolylmethylamines (Shoesmith and Slater, J., 1924, **125**, 2278).

EXPERIMENTAL.

Three series of reactions by which the isomeric β-methoxyphenylethyl alcohols might conceivably be prepared were investigated :

(1) $R\cdot CHO \xrightarrow{CH_2(CO_2H)_2} CHR{:}CH\cdot CO_2H \xrightarrow[\text{amalg.}]{Na} CH_2R\cdot CH_2\cdot CO_2H \xrightarrow[+NH_3]{SOCl_2} CH_2R\cdot CH_2\cdot CONH_2 \xrightarrow{NaOCl} CH_2R\cdot CH_2\cdot NH_2 \xrightarrow{HNO_2} CH_2R\cdot CH_2\cdot OH$ (Haworth, Perkin, and Rankin, J., 1924, **125**, 169).

(2) $R\cdot CHO \xrightarrow[+\text{alkali}]{CH_3NO_2} CHR{:}CH\cdot NO_2 \xrightarrow[\text{acid}]{Zn\,+} CH_2R\cdot CH{:}NOH \xrightarrow[\text{amalg.}]{Na} CH_2R\cdot CH_2\cdot NH_2 \longrightarrow CH_2R\cdot CH_2\cdot OH$ (Rosenmund, *Ber.*, 1909, **42**, 4778).

(3) $R\cdot Br \xrightarrow[CH_2Cl\cdot CH_2OH]{Mg\,+} CH_2R\cdot CH_2\cdot OH$ (Grignard, *Compt. rend.*, 1905, **141**, 44).

The yield of amine obtained by scheme (1) was much better than that by (2), but the poor yield of alcohol from amine led to the adoption of (3), which involved the laborious preparation of large quantities of the isomeric bromoanisoles.

The following is the best method for the preparation of *o*-methoxybenzaldehyde [used in (1) and (2)] in quantity : Salicylaldehyde (122 g.) was emulsified in a flask fitted with a reflux condenser by vigorous stirring with 40 c.c. of water, and a solution of potassium hydroxide (85 g. in 160 c.c. of water) added alternately with methyl sulphate (157 g.). The appearance and disappearance of the yellow colour of the potassium compound of the aldehyde served as an excellent indication of the course of the reaction; excess of alkali was avoided and hence the reaction temperature could be allowed to rise without affecting the yield, which was always about 100 g., b. p. 236—237°.

The amines obtained in series (1) had b.p.'s as follows: $R = C_6H_5$, 88—89°/18 mm.; $R = o\text{-MeO·}C_6H_4$, 127—128°/21 mm.; $R = m\text{-MeO·}C_6H_4$, 126—127°/14 mm.; $R = p\text{-MeO·}C_6H_4$, 131—132°/18 mm.

Action of Nitrous Acid on β-Phenylethylamine in Hydrochloric Acid Solution.—The amine hydrochloride, precipitated from a benzene solution of the amine by hydrogen chloride, was dissolved in a small quantity of water, and dilute hydrochloric acid added, followed by an aqueous solution of sodium nitrite. The whole was allowed to stand for 2 hours and the reaction was completed by 30 minutes' heating on the water-bath. The oil was extracted with ether, washed, dried, and distilled, the lowest fraction, b. p. 82—87°/21 mm., being collected separately. It was a colourless, non-pungent oil, containing hydrolysable chlorine, and when treated with fuming nitric acid at —15° (compare Barger, J., 1909, **95**, 2193) it yielded β-*p*-nitrophenylethyl chloride, m. p. 46—47°, unaltered by admixture with an authentic specimen. When sulphuric acid was employed in place of hydrochloric acid only very small, impure yields were obtained.

As examples of the methods used in scheme (2), the following are given, since the compounds have not been previously described.

m-*Methoxy-ω-nitrostyrene.*—To a vigorously stirred solution of *m*-methoxybenzaldehyde (28 g.) and nitromethane (13 g.) in alcohol (40 c.c.), 25% methyl-alcoholic potassium hydroxide (23 c.c.) was slowly added, followed by a solution of sodium hydroxide (4 g. in 20 c.c. of water), after which the almost solid product was poured into ice-water and, when *completely in solution*, decomposed with the calculated quantity of ice-cold sulphuric acid; the crude yellow m-*methoxy-ω-nitrostyrene* was filtered, washed, and dried. It crystallised from alcohol in light yellow plates, m. p. 93—94° (Found: N, 8·0. $C_9H_9NO_3$ requires N, 7·8%).

The nitrostyrene (13 g.) was mixed with zinc dust (13 g.) and the mixture added to a vigorously stirred solution of 25 c.c. of glacial acetic acid in 65 c.c. of alcohol, the temperature being kept at 35°. After 10 minutes, alcohol (20 c.c.) was added, and when the temperature had fallen to 15° the solid was filtered off and extracted with ether; the extract was washed with aqueous sodium carbonate and then extracted with sodium hydroxide. m-*Methoxyphenylacetaldoxime* was precipitated from this on the addition of sodium bicarbonate, and was filtered, washed, dried, and recrystallised from ligroin, and finally from water; white needles, m. p. 92·5—93° (Found: N, 8·5. $C_9H_{11}NO_2$ requires N, 8·5%).

From this oxime in alcoholic acetic acid only a very small quantity of β-*m*-methoxyphenylethylamine could be obtained by the action of 3% sodium amalgam.

Action of Phosphorus Pentabromide on β-o-*Methoxyphenylethyl Alcohol.*—*o*-Bromoanisole, b. p. 220°/744 mm., prepared by the action of methyl sulphate on *o*-bromophenol, was converted into β-o-*methoxyphenylethyl alcohol* in the manner already described (Shoesmith and Connor, *loc. cit.*). It is a colourless liquid, b. p. 130—131°/11 mm. (Found: C, 71·8; H, 7·77. $C_9H_{12}O_2$ requires C, 71·1; H, 7·9%). The alcohol (10 g.) was slowly added to phosphorus pentabromide (35 g.) in dry benzene (50 c.c.), the whole being cooled in ice-water. After 30 minutes, dry air was slowly drawn through the solution for 4 hours during which time the pentabromide slowly disappeared. The solution was then washed with ice-water, dried, the benzene distilled, and the residue fractionated under diminished pressure. No definite fraction could be separated other than one at 160—165°/12 mm., which solidified and crystallised from alcohol in fine, non-pungent, white needles of β-5-*bromo*-2-*methoxyphenylethyl bromide*, m. p. 55° [Found: C, 36·9; H, 3·5; Br (total), 53·7; Br (hydrolysable), 27·2. $C_9H_{10}OBr_2$ requires C, 36·7; H, 3·4; Br (total), 54·4; Br (hydrolysable), 27·2%].

The compound resisted oxidation with alkaline permanganate but was oxidised finally according to the scheme $CH_2R{\cdot}CH_2Br \xrightarrow[KOH]{alc.} CHR{:}CH_2 \xrightarrow[+H_2SO_4]{K_2Cr_2O_7} R{\cdot}CO_2H$. Approximately 0·5 g. of the bromide was heated on the water-bath for 30 minutes with 5 c.c. of 20% alcoholic potassium hydroxide; the whole was diluted with water, extracted with ether, the ether distilled, and the residue boiled for 3 hours with 1·2 g. of potassium dichromate and 7 c.c. of 20% sulphuric acid; the resinous oxidation product was separated and boiled with aqueous sodium hydroxide, excess of dilute hydrochloric acid was added, the liberated acid was extracted with ether, and the ether solution in turn extracted with sodium carbonate, from which on acidification and ether-extraction an acid was obtained. Recrystallised from water, it had m. p. 118—119°. 5-Bromo-2-methoxybenzoic acid has m. p. 119° (compare *Gazzetta*, 1886, **16**, 408). This established the constitution of the bromide as above.

Action of Phosphorus Pentabromide on β-m-*Methoxyphenylethyl Alcohol.*—*m*-Bromonitrobenzene was reduced to *m*-bromoaniline by West's method (J., 1925, **127**, 994) and converted into *m*-bromophenol (compare B.P. 200714)—for the necessary details of this process we are greatly indebted to Dr. H. H. Hodgson. This phenol with methyl sulphate gave *m*-bromoanisole, b. p. 214°/729 mm., which was then converted into β-m-*methoxyphenylethyl alcohol* in the usual manner. The alcohol is a colourless liquid, b. p. 135—137°/12 mm. (Found : C, 71·1 ; H, 7·6%).

When the alcohol was treated with phosphorus pentabromide, as in the previous case, no definite fraction could be separated, but when excess of pentabromide was used in the cold, a colourless, non-lachrymatory, non-pungent oil, b. p. 163—165°/13 mm., was isolated [Found : Br (total), 53·8 ; Br (hydrolysable), 27·2%]. The compound was oxidised much more readily than its isomeride, and gave an acid, m. p. 160—161°, which did not depress the m. p. of an authentic sample of 6-bromo-3-methoxybenzoic acid (J., 1925, **127**, 880), kindly supplied by Dr. H. H. Hodgson. This characterised the oil as β-6-*bromo*-3-*methoxyphenylethyl bromide.*

Action of Phosphorus Pentabromide on β-p-*Methoxyphenylethyl Alcohol.*—The alcohol was obtained from *p*-bromoanisole in the usual manner, and when purified had b. p. 138—140°/11 mm., m. p. 24° (compare Grignard, *loc. cit.*). When 1 mol. of pentabromide was used per mol. of alcohol, a colourless oil, b. p. 130—131°/11 mm., was obtained, which was almost pure β-p-*methoxyphenylethyl bromide* [Found : Br (hydrolysable), 35·0. $C_9H_{11}OBr$ requires Br (hydrolysable), 37·2%]. It was non-pungent and non-lachrymatory, and very similar in properties to the β-tolylethyl bromides (Shoesmith and Connor, *loc. cit.*), but further fractionation produced no improvement in the quality of the sample. With excess of pentabromide a colourless oil of b. p. 187—188°/19 mm. was formed [Found : Br (hydrolysable), 27·0%]. From this oil an acid of m. p. 217° was obtained on oxidation. 3-Bromo-4-methoxybenzoic acid has m. p. 218° (Balbiano, *Gazzetta*, 1881, **11**, 406), and the oil was therefore β-3-*bromo*-4-*methoxyphenylethyl bromide.*

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