434. *Preparation of β-Phenoxypropionic Acids by the Reaction of Phenols with Ethyl Acrylate.*

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A number of β-halogenophenoxypropionic acids is prepared by the condensation of halogenophenols and ethyl acrylate in presence of sodium and direct hydrolysis of the reaction mixture with cold aqueous alkali.

Recently Rehberg, Dixon, and Fisher reported (*J. Amer. Chem. Soc.*, 1947, **69**, 2966; 1946, **68**, 544) that under mild, alkaline, anhydrous conditions primary and secondary, but not tertiary, aliphatic alcohols readily add to the olefinic linkage of alkyl acrylates, giving good yields

of β-alkoxypropionates. In the present paper the condensation of phenol and halogenophenols with ethyl acrylate is used to prepare the corresponding β-phenoxy- and β-halogenophenoxy-propionic acids, some of which have previously been synthesised by other methods.

$$CH_2{:}CH{\cdot}CO_2Et + ROH \longrightarrow RO{\cdot}CH_2{\cdot}CH_2{\cdot}CO_2Et$$

Thus β-phenoxypropionic acid has been prepared by treating sodium or potassium phenoxide with a β-halogenopropionic acid (Bischoff, *Ber.*, 1900, **33**, 924; Arndt and Källner, *ibid.*, 1924, **57**, 202), or by oxidising 3-phenoxypropan-1-ol (Powell, *J. Amer. Chem. Soc.*, 1923, **45**, 2708); these methods have been applied in the preparation of substituted phenoxypropionic acids, *e.g.*, by Chakravarti and Dutta (*J. Indian Chem. Soc.*, 1939, **16**, 639) and by Synerholm and Zimmermann (*Contrib. Boyce Thompson Inst.*, 1947, **14**, 369), respectively. β-*p*-Chlorophenoxypropionic acid has also been prepared by chlorinating β-phenoxypropionic acid (Haskelberg, *J. Org. Chem.*, 1947, **12**, 426). After the present work had been completed, Gresham, Jansen, Shaver, Bankert, Beears, and Prendergast (*J. Amer. Chem. Soc.*, 1949, **71**, 661; cf. Gresham and Shaver, U.S.P. 2,449,991; *Chem. Abs.*, 1949, **43**, 1053) reported the preparation of a number of substituted β-phenoxypropionic acids by interaction of β-propionolactone with phenols and their salts. As far as could be ascertained, the only references to the direct condensation of phenol and an ester of acrylic acid are D.R.-P. 670,357 (I.G. Farbenind. A.-G. and H. Ufer) and the equivalent F.P. 833,734, which claim the addition of aromatic hydroxy-compounds to derivatives of acrylic acid.

It has now been found that phenol and substituted phenols add to the olefinic linkage of ethyl acrylate under more drastic conditions than those required for aliphatic alcohols. Temperatures between 95° and 110° were generally satisfactory. As only small samples of the substituted β-phenoxypropionic acids prepared were required for other purposes the reactions were carried out under standard, not necessarily optimal, conditions. Considerable improvements in yields could no doubt be effected, as most of the unchanged acrylate and phenol was recovered.

The β-phenoxypropionic esters which were the primary reaction products were isolated in the first experiments and found to be extremely readily hydrolysed by aqueous alkali; in working up the subsequent reaction mixtures it was convenient, therefore, to add concentrated aqueous sodium hydroxide to convert the esters, at least in part, into the corresponding acids which could thus be obtained directly. The acids were characterised as the amides; the *ethyl* esters were low-melting solids, although ethyl β-phenoxypropionate, the only one previously prepared, was described as an oil.

Experimental.

All m. p.s are uncorrected. Microanalyses are by Drs. Weiler and Strauss of Oxford.

β-Phenoxypropionic Acid.—Metallic sodium (0·5 g.) was dissolved in "AnalaR" phenol (47 g.), m. p. 41°, and ethyl acrylate (50 g.), b. p. 99°, n_D^{18} 1·4046 (purity, ~95%), containing quinol (0·1 g.) was added. The mixture was heated at 95—110° for 40 hours; when cool it was diluted with water (100 ml.) containing acetic acid (0·5 ml.). Ether-extraction, drying (Na_2SO_4), and removal of the ether and unchanged ethyl acrylate under reduced pressure afforded a viscous oil which was separated by fractional distillation into unchanged phenol (23 g.), b. p. 75°/11 mm., which solidified on seeding, and ethyl β-phenoxypropionate (48 g.), b. p. 142°/11 mm., n_D^{18} 1·5007, which solidified when kept and then crystallised from light petroleum (b. p. 40—60°) in needles, m. p. 24° (sap. val., 291. Calc. for $C_{11}H_{14}O_3$: sap. val., 289) (Koelsch, *J. Amer. Chem. Soc.*, 1930, **52**, 2430, gives b. p. 175—177°/50 mm., and n_D^{25} 1·5055). Hydrolysis of the ester (1 g.) with a N-solution of potassium hydroxide in 50% aqueous ethanol (25 ml.) at room temperature was complete in about 5 minutes and gave β-phenoxypropionic acid (0·7 g.) which crystallised from aqueous methanol in leaflets, m. p. 97—98° (equiv., by titration with 0·05N-potassium hydroxide, 169. Calc. for $C_9H_{10}O_3$, 166) (Powell, *loc. cit.*, gives m. p. 98°, Koelsch, *loc. cit.*, m. p. 96—97°, and Gresham *et al.*, *loc. cit.*, m. p. 94—95°). Treating the acid with excess of thionyl chloride in the cold and pouring into concentrated aqueous ammonia at 0° gave β-phenoxypropionamide, which crystallised from aqueous methanol in needles, m. p. 119° (Powell, *loc. cit.*, gives m. p. 119°).

β-p-Chlorophenoxypropionic Acid.—(*a*) Use of *p*-chlorophenol (64·5 g.), m. p. 40—41°, instead of phenol in the above reaction led to *ethyl* β-p-*chlorophenoxypropionate* (44 g.), b. p. 90°/0·2 mm., n_D^{17} 1·5134, which solidified on standing and then crystallised from light petroleum (b. p. 40—60°) in needles, m. p. 34—35° (Found: C, 58·2; H, 5·95; Cl, 15·55. $C_{11}H_{13}O_3Cl$ requires C, 57·8; H, 5·7; Cl, 15·5%). The ester on hydrolysis as before gave β-*p*-chlorophenoxypropionic acid, which crystallised from aqueous methanol in fine plates, which melted sharply at 135·5° (Chakravarti and Dutta, *loc. cit.*, give m. p. 138—139°, Haskelberg, *loc. cit.*, m. p. 139°, and Gresham *et al.*, *loc. cit.*, m. p. 134—135°).

(*b*) This acid (38 g.) was also obtained by condensing *p*-chlorophenol and ethyl acrylate over sodium as above, diluting the reaction mixture with ether (150 ml.), shaking (5 minutes) thrice with 25% aqueous sodium hydroxide (50 ml. each time), and acidifying the aqueous layers with concentrated hydrochloric acid. The viscous oil so obtained contained the desired acid and unchanged *p*-chlorophenol; it was dissolved in ether and extracted with saturated aqueous sodium hydrogen carbonate; the acid (38 g.) was precipitated on acidification of the aqueous layer. *β-p-Chlorophenoxypropionamide,*

prepared from the acid in the usual manner, crystallised from 2N-ammonia, containing a little methanol, in needles, m. p. 136—137° (Found : C, 53·8; H, 5·15; N, 6·7. $C_9H_{10}O_2NCl$ requires C, 54·15; H, 5·05; N, 7·0%). The original ethereal solution remaining after extraction with sodium hydroxide was evaporated and gave ethyl β-*p*-chlorophenoxypropionate (6 g.) which had not been hydrolysed and was identical with the ester obtained by method (*a*).

β-o-*Chlorophenoxypropionic Acid.*—Reaction of *o*-chlorophenol (64 g.), b. p. 92°/55 mm., n_D^{20} 1·5580, with ethyl acrylate (50 g.) by method (*b*) gave *ethyl* β-o-*chlorophenoxypropionate* (12 g.), b. p. 87°/0·1 mm., n_D^{20} 1·5130 (Found : C, 57·95; H, 5·95. $C_{11}H_{13}O_3Cl$ requires C, 57·8; H, 5·7%), which crystallised from light petroleum, cooled in acetone containing solid carbon dioxide, in needles, m. p. 2·5—4·5°, and β-*o*-chlorophenoxypropionic acid (7·5 g.) which crystallised from aqueous methanol in needles, m. p. 111° (Chakravarti and Dutta, *loc. cit.*, give m. p. 108—109°, and Gresham *et al.*, *loc. cit.*, m. p. 112—113°). The acid was characterised as β-o-*chlorophenoxypropionamide*, which crystallised from 2N-ammonia containing a little methanol in leaflets, m. p. 90° (Found : C, 53·75; H, 5·2; N, 6·55. $C_9H_{10}O_2NCl$ requires C, 54·15; H, 5·05; N, 7·0%).

β-2 : 4-*Dichlorophenoxypropionic Acid.*—By method (*b*) 2 : 4-dichlorophenol (80 g.), m. p. 45°, and ethyl acrylate (50 g.) gave *ethyl* β-2 : 4-*dichlorophenoxypropionate* (8 g.), b. p. 115°/0·1 mm., n_D^{20} 1·5149 (Found : C, 50·55; H, 4·85. $C_{11}H_{12}O_3Cl_2$ requires C, 50·2; H, 4·6%), which crystallised from light petroleum in needles, m. p. 16—17°, and β-2 : 4-dichlorophenoxypropionic acid (25 g.) which crystallised from aqueous methanol in needles, m. p. 92—93° (Synerholm and Zimmermann, *loc. cit.*, give m. p. 93°, and Gresham *et al.*, *loc. cit.*, m. p. 91—92°). The acid was converted into the amide which on slow crystallisation from aqueous methanol gave leaflets, m. p. 104° (Synerholm and Zimmermann, *loc. cit.*, give m. p. 104°).

β-4-*Chloro*-2-*methylphenoxypropionic Acid.*—5-Chloro-*o*-cresol (42 g.), m. p. 48° (obtained from *o*-cresol and sulphuryl chloride by the method of Sah and Anderson, *J. Amer. Chem. Soc.*, 1941, **63**, 3164), with ethyl acrylate (25 g.) [method (*b*)] gave *ethyl* β-4-*chloro*-2-*methylphenoxypropionate* (10 g.), b. p. 84°/0·3 mm., n_D^{20} 1·5102, which solidified on standing and then crystallised from light petroleum in needles, m. p. 22·5—23·5° (Found : C, 59·75; H, 6·1. $C_{12}H_{15}O_3Cl$ requires C, 59·4; H, 6·25%), and β-4-*chloro*-2-*methylphenoxypropionic acid* (22 g.) which crystallised from aqueous methanol in needles, m. p. 104° (Found : C, 56·1; H, 5·4. $C_{10}H_{11}O_3Cl$ requires C, 55·95; H, 5·2%). The *amide* crystallised from aqueous methanol in needles, m. p. 94° (Found : C, 56·5; H, 5·9; N, 6·75. $C_{10}H_{12}O_2NCl$ requires C, 56·2; H, 5·65; N, 6·55%).

β-4-*Chloro*-3-*methylphenoxypropionic Acid.*—6-Chloro-*m*-cresol (72 g.), m. p. 66° (obtained from *m*-cresol and sulphuryl chloride using the procedure of Sah and Anderson, *loc. cit.*), with ethyl acrylate (50 g.) [method (*b*)] gave *ethyl* β-4-*chloro*-3-*methylphenoxypropionate* (10 g.), b. p. 96·5—97°/0·1 mm., n_D^{20} 1·5144, which solidified on storage, and on crystallisation from light petroleum had m. p. 31—32° (Found : C, 59·65; H, 6·3; Cl, 14·9. $C_{12}H_{15}O_3Cl$ requires C, 59·4; H, 6·25; Cl, 14·6%), and β-4-*chloro*-3-*methylphenoxypropionic acid* (33·5 g.) which crystallised from aqueous methanol in needles, m. p. 142° (Found : C, 56·2; H, 5·3. $C_{10}H_{11}O_3Cl$ requires C, 55·95; H, 5·2%). The derived *amide* crystallised from aqueous methanol in leaflets, m. p. 113° (Found : C, 56·3; H, 5·75; N, 6·7. $C_{10}H_{12}O_2NCl$ requires C, 56·2; H, 5·65; N, 6·55%).

β-2-*Chloro*-4-*methylphenoxypropionic Acid.*—3-Chloro-*p*-cresol (72 g.), b. p. 195—197°, n_D^{20} 1·5531 (prepared from *p*-cresol by the method of Sah and Anderson, *loc. cit.*, who give b. p. 195—197°, n_D^{27} 1·5200), and ethyl acrylate (50 g.) [method (*b*)] gave *ethyl* β-2-*chloro*-4-*methylphenoxypropionate* (26·5 g.), b. p. 95°/0·1 mm., n_D^{20} 1·5130, which crystallised from light petroleum (cooled in acetone containing solid carbon dioxide) in needles, m. p. 14—14·5° (Found : C, 59·7; H, 6·25; Cl, 14·3. $C_{12}H_{15}O_3Cl$ requires C, 59·4; H, 6·25; Cl, 14·6%), and β-2-*chloro*-4-*methylphenoxypropionic acid* (20 g.) which crystallised from aqueous methanol in needles, m. p. 129° (Found : C, 55·9; H, 5·3. $C_{10}H_{11}O_3Cl$ requires C, 55·95; H, 5·2%). The *amide* crystallised from 2N-ammonia, containing methanol, in leaflets, m. p. 112° (Found : C, 56·15; H, 5·75; N, 6·8. $C_{10}H_{12}O_2NCl$ requires C, 56·2; H, 5·65; N, 6·55%).

β-p-*Bromophenoxypropionic Acid.*—*p*-Bromophenol (86 g.), m. p. 63°, and ethyl acrylate (50 g.) [method (*b*)] gave *ethyl* β-p-*bromophenoxypropionate* (5 g.), b. p. 134°/0·2 mm., n_D^{20} 1·5308, which solidified when kept and after crystallisation from light petroleum had m. p. 44° (Found : C, 48·65; H, 4·9. $C_{11}H_{13}O_3Br$ requires C, 48·4; H, 4·8%), and β-*p*-bromophenoxypropionic acid (25 g.) which crystallised from methanol in plates, m. p. 144—145° (Gresham *et al.*, *loc. cit.*, give m. p. 142—143°) (Found : C, 44·6; H, 3·4; Br, 32·0. Calc. for $C_9H_9O_3Br$: C, 44·1; H, 3·7; Br, 32·6%). The *amide* crystallised from aqueous methanol in needles, m. p. 136° (Found : C, 44·8; H, 4·25; N, 5·4. $C_9H_{10}O_2NBr$ requires C, 44·3; H, 4·15; N, 5·7%).

β-o-*Bromophenoxypropionic Acid.*—*o*-Bromophenol (24 g.), n_D^{20} 1·5844, and ethyl acrylate (14 g.) [method (*b*)] gave *ethyl* β-o-*bromophenoxypropionate* (5 g.), b. p. 108°/0·1 mm., n_D^{20} 1·5291, which crystallised from light petroleum (cooled in acetone containing solid carbon dioxide) in needles, m. p. 11—12° (Found : C, 49·0; H, 5·0; Br, 29·4. $C_{11}H_{13}O_3Br$ requires C, 48·4; H, 4·8; Br, 29·25%), and β-*o*-bromophenoxypropionic acid, plates, m. p. 109·5—110°, from aqueous methanol (Gresham *et al.*, *loc. cit.*, give m. p. 109—110°) (Found : C, 44·5; H, 3·9. Calc. for $C_9H_9O_3Br$: C, 44·1; H, 3·7%). The *amide* crystallised from methanol–2N-aqueous ammonia in needles, m. p. 117° (Found : C, 44·9; H, 4·25; N, 5·55. $C_9H_{10}O_2NBr$ requires C, 44·3; H, 4·15; N, 5·7%).

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