The Bromination of o- *and* p-*Hydroxyaryl Ketones.*

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2-Hydroxyacetophenone, 2-hydroxypropiophenone, and similar ketones, like their *p*-isomers, undergo predominantly side-chain substitution with bromine in anhydrous acetic acid and nuclear substitution in aqueous acetic acid. However, hydroxyaryl ketones of high molecular weight, such as 4-hydroxystearophenone, polyhydroxy-ketones, such as respropiophenone, and hydroxynaphthyl ketones, such as 2- and 4-acetyl-1-naphthol, undergo only nuclear monobromination.

It has generally been assumed that hydroxyaryl ketones undergo nuclear substitution with free bromine, and that side-chain bromination occurs only when the positions *ortho* and *para* to the hydroxy-groups are blocked. However, it was recently found (Buu-Hoï, Xuong, and Lavit, *J.*, 1954, 1034) that 4-hydroxy-acetophenone and -propiophenone underwent side-chain bromination in anhydrous acetic acid, and nuclear bromination in aqueous acetic acid. These studies have now been extended to other hydroxy-ketones.

With 1 mol. of bromine, 2-hydroxy-acetophenone and -propiophenone gave ω-bromo-2-hydroxyacetophenone and α-bromo-2-hydroxypropiophenone in anhydrous acetic acid; in aqueous acetic acid, 5-bromo-2-hydroxy-acetophenone and -propiophenone were obtained. Yields in these and similar side-chain brominations were far from quantitative, but, although nuclear substitution may have occurred to a small extent, no such product could be isolated. Further substitution affected the nucleus in both solvents, as shown by the formation of 3 : 5-dibromo-2-hydroxypropiophenone from 2-hydroxypropiophenone and 2 mols. of bromine in aqueous acetic acid, and of α : 5-dibromo-2-hydroxypropiophenone in anhydrous acetic acid; 2-hydroxyacetophenone gave similar results. The same behaviour was observed with 5-fluoro-2-hydroxypropiophenone, which was monobrominated in the side-chain in anhydrous acetic acid, and with 2-hydroxy-5-methylacetophenone, which gave ω- or 3-bromo- or 3 : ω-dibromo-2-hydroxy-5-methylacetophenone according to the experimental conditions.

With hydroxy-ketones derived from higher fatty acids, no side-chain bromination occurred, probably on account of steric hindrance (cf. Buu-Hoï *et al.*, *Rec. Trav. chim.*, 1947, **66**, 308; *J.*, 1946, 795; 1948, 106); 4-hydroxystearophenone, for instance, gave the 3-bromo-derivative with 1 mol. of bromine, and the 3 : 5-dibromo-derivative with 2 mols. in anhydrous or aqueous acetic acid. Further, respropiophenone (2 : 4-dihydroxypropiophenone) gave the 3 : 5-dibromo-derivative with 1 or 2 mols. of bromine in either solvent; and in confirmation of Hantzsch's finding (*Ber.*, 1906, **39**, 3097), monobromination of 2-acetyl-1-naphthol in anhydrous acetic acid afforded the 4-bromo-naphthol, and dibromination yielded the 4 : ω-dibromo-compound (Fries and Frellstedt, *Ber.*, 1921, **54**, 720). 4-Acetyl-1-naphthol similarly gave 4-acetyl-2-bromo-1-naphthol with 1 mol. of bromine.

The selective nuclear brominations in aqueous acetic acid observed here are in line with the observations of Robertson *et al.* (*J.*, 1943, 276, 279; 1947, 1167; 1948, 100; 1949, 294, 933) that the rates of aromatic halogenation are very much increased by the presence of water, and that " ionisation of the halogen–halogen bond occurs during, rather than before, association with the aromatic nucleus " (cf. Braude, *Ann. Reports*, 1949, **46**, 138). Throughout the present work, nuclear was much faster than side-chain bromination.

Structures of the ω-bromo-ketones were proved by conversion into coumaranones by mild alkali (Friedländer and Neudörfer, *Ber.*, 1897, **30**, 1081; Fries *et al.*, *Ber.*, 1908, **41**, 4278; 1910, **43**, 215), or more conveniently by Hinsberg reactions (*Annalen*, 1896, **292**, 246; Buu-Hoï and Khôi, *Bull. Soc. chim.*, 1950, **17**, 753) with *o*-phenylenediamine to give 2-hydroxyarylquinoxalines.

Experimental

ω-Bromo-2-hydroxyacetophenone.—To a solution of *o*-hydroxyacetophenone (16 g.; prepared by Fries rearrangement of phenyl acetate) in glacial acetic acid (200 c.c.), a solution of bromine (18·5 g.) in the same solvent (50 c.c.) was added dropwise (3 hr.) with shaking; after decolor-

ation, the solution was diluted with water and the oil taken up in chloroform, washed, and dried (Na_2SO_4); the solvent was evaporated and the residue fractionated *in vacuo*; the *bromo-ketone* (12 g.), b. p. 152—158°/18 mm., n_D^{25} 1·6168, formed yellowish needles, m. p. 45°, from light petroleum (Found: C, 44·5; H, 3·5. $C_8H_7O_2Br$ requires C, 44·7; H, 3·3%). The constitution was determined by 2 hours' refluxing of this ketone (2 g.) and sodium acetate (2 g.) in ethanol (30 c.c.); the precipitate of coumaranone formed on dilution with water crystallised as pale yellow needles, m. p. 101°, from methanol (lit., m. p. 101—102°). The forerun from the bromination product consisted of *o*-hydroxyacetophenone, and recrystallisation of the higher-boiling fraction gave ω: *5-dibromo-2-hydroxyacetophenone* (0·5 g.), yellowish prisms, m. p. 107°, from acetic acid (Found: C, 32·8; H, 2·3. $C_8H_6O_2Br_2$ requires C, 32·7; H, 2·0%); the same compound was obtained in almost theoretical yield from bromine (1 mol.) and either ω-bromo-2-hydroxyacetophenone in 50% aqueous acetic acid, or 5-bromo-2-hydroxyacetophenone in glacial acetic acid.

ω-Bromo-2-hydroxyacetophenone (3 g.), *o*-phenylenediamine (1·5 g.), and sodium acetate (2 g.) in ethanol (50 c.c.) were refluxed for 2 hr.; the precipitate of 2-o-*hydroxyphenylquinoxaline* obtained on cooling formed orange-yellow, sublimable needles (3 g.), m. p. 191°, from ethanol (Found: C, 75·4; H, 4·5; N, 12·4. $C_{14}H_{10}ON_2$ requires C, 75·7; H, 4·5; N, 12·6%).

Nuclear Bromination of o-*Hydroxyacetophenone.*—(*a*) To a solution of this ketone (5 g.) in 50% aqueous acetic acid (50 c.c.), bromine (5·8 g.) in 80% aqueous acetic acid (25 c.c.) was added in small portions with shaking. The oil formed on dilution with water was taken up in chloroform, washed with water, dried (Na_2SO_4), and purified by vacuum-distillation, giving 5-bromo-2-hydroxyacetophenone (5 g.), b. p. 145—148°/20 mm., which formed colourless needles, m. p. 62° (Found: Br, 37·3. Calc. for $C_8H_7O_2Br$: Br, 37·2%); Kostanecki and Ludwig (*Ber.*, 1898, **31**, 2953) gave m. p. 61—62°.

(*b*) A solution of *o*-hydroxyacetophenone (3 g.) in 50% aqueous acetic acid (50 c.c.) was treated with bromine (7 g.), dissolved in 80% aqueous acetic acid, in small portions. The mixture was then heated at 65° to decoloration, water was added, and the solid precipitate recrystallised from aqueous acetic acid; 3: *5-dibromo-2-hydroxyacetophenone* formed pale yellow needles (4 g.), m. p. 111° (Found: Br, 54·1. $C_8H_6O_2Br_2$ requires Br, 54·4%).

Bromination of o-*Hydroxypropiophenone.*—(*a*) *o*-Hydroxypropiophenone (10 g.; n_D^{25} 1·550) in 65% aqueous acetic acid (150 c.c.) was treated with bromine (10·7 g.), dissolved in 80% aqueous acetic acid, at room temperature; *5-bromo-2-hydroxypropiophenone*, obtained on dilution with water, crystallised as yellowish needles (10 g.), m. p. 77°, from methanol (Found: C, 47·5; H, 3·8. $C_9H_9O_2Br$ requires C, 47·2; H, 3·9%).

(*b*) *o*-Hydroxypropiophenone (10 g.) in anhydrous acetic acid (140 c.c.) was cooled in ice-water and treated dropwise (2 hr.) with bromine (10·6 g.) in the same solvent; the oil formed on dilution with water was taken up in chloroform and vacuum-distilled, giving *α-bromo-2-hydroxypropiophenone* as a pale yellow, lachrymatory oil (6 g.), b. p. 145—150°/15 mm., $n_D^{22\cdot5}$ 1·5930 (Found: C, 47·0; H, 3·8%). Its constitution was determined by removal of bromine with hot aniline and conversion into 2-methylcoumaranone, b. p. 122°/16 mm., n_D^{25} 1·5650, by sodium acetate in hot ethanol [Störmer and Atenstädt (*Ber.*, 1902, **35**, 3565) gave b. p. 163—165°/40 mm.; von Auwers (*Ber.*, 1919, **52**, 121; *Annalen*, 1912, **393**, 360) gave $n_D^{19\cdot7}$ 1·5630, b. p. 119°/15—16 mm.].

(*c*) *o*-Hydroxypropiophenone (10 g.) in 65% aqueous acetic acid (150 c.c.) with bromine (21·4 g.) in 80% aqueous acetic acid yielded 3: *5-dibromo-2-hydroxypropiophenone* (11 g.), pale yellow needles, m. p. 118° (from methanol) (Found: C, 35·0; H, 2·8. $C_9H_8O_2Br_2$ requires C, 35·1; H, 2·6%).

(*d*) Bromination (2 mols. of halogen) in anhydrous acetic acid gave 5: *α-dibromo-2-hydroxypropiophenone* (10 g.), yellowish prisms, m. p. 99° (from ethanol) (Found: C, 34·7; H, 2·7%); the same compound was obtained on monobromination of 5-bromo-2-hydroxypropiophenone in anhydrous acetic acid. The presence of a labile bromine atom was shown by the formation of aniline hydrobromide with hot aniline.

α-Bromo-5-fluoro-2-hydroxypropiophenone.—5-Fluoro-2-hydroxypropiophenone (6·5 g.) with bromine (6·2 g.) in anhydrous acetic acid (100 c.c.) gave a *bromo-compound* (5 g.), b. p. 147°/16 mm., n_D^{26} 1·5748, yellowish prisms, m. p. 48° (from light petroleum) (Found: C, 43·4; H, 3·2. $C_9H_8O_2BrF$ requires C, 43·7; H, 3·2%).

Bromination of 4-*Hydroxystearophenone.*—(*a*) The ketone (2·5 g.) in anhydrous acetic acid (350 c.c.) with bromine (1·1 g.) gave *3-bromo-4-hydroxystearophenone* (2·5 g.), colourless needles, m. p. 96° (from aqueous acetic acid) (Found: C, 65·2; H, 8·9. $C_{21}H_{39}O_2Br$ requires C, 65·6; H, 8·9%).

(*b*) Similar treatment with double the amount of bromine yielded 3 : 5-*dibromo*-4-*hydroxystearophenone* (3 g.), colourless leaflets, m. p. 80° (from acetic acid) (Found : C, 55·3; H, 7·3. $C_{24}H_{38}O_2Br_2$ requires C, 55·6; H, 7·3%). The same compound was obtained by bromination in aqueous acetic acid.

Bromination of 2-*Hydroxy*-5-*methylacetophenone*.—(*a*) 2-Hydroxy-5-methylacetophenone (20 g.) in anhydrous acetic acid was treated with bromine (21·3 g.); after 7 hr., water was added, and the product taken up in chloroform and purified by vacuum-distillation. *ω-Bromo*-2-*hydroxy*-5-*methylacetophenone* (12 g.) was formed as a pale yellow, lachrymatory oil, n_D^{26} 1·6023 (Found : C, 46·9; H, 3·7. $C_9H_9O_2Br$ requires C, 47·2; H, 3·9%). This compound (5 g.) with *o*-phenylenediamine (2·4 g.) and sodium acetate (3 g.) in ethanol (50 c.c.), refluxed for 2 hr., gave 2-(2-*hydroxy*-5-*methylphenyl*)*quinoxaline* (4 g.), yellow, sublimable needles, m. p. 198° (from ethanol) (Found : C, 76·0; H, 5·2. $C_{15}H_{12}ON_2$ requires C, 76·3; H, 5·1%).

(*b*) The ketone (10 g.) in 50% aqueous acetic acid (120 c.c.) with bromine (10·6 g.) in 80% aqueous acetic acid gave 3-*bromo*-2-*hydroxy*-5-*methylacetophenone* (10 g.), yellowish needles (from methanol), m. p. 89° (Found : C, 47·0; H, 4·0%).

3 : *ω-Dibromo*-2-*hydroxy*-5-*methylacetophenone*.—Obtained by treating ω-bromo-2-hydroxy-5-methylacetophenone (3·7 g.) in 50% aqueous acetic acid at 60° with bromine (2·6 g.; 75% yield), or 2-hydroxy-5-methylacetophenone (5 g.) in anhydrous acetic acid with bromine (10·6 g.; 55% yield), this *ketone* crystallised as pale yellow needles, m. p. 106°, from aqueous acetic acid (Found : C, 34·8; H, 2·7. $C_9H_8O_2Br_2$ requires C, 35·1; H, 2·6%).

This ketone (3 g.), *o*-phenylenediamine (1 g.), and sodium acetate (1·3 g.) in ethanol (70 c.c.) were refluxed for 3 hr. The precipitate gave on recrystallisation from benzene 2-(3-*bromo*-2-*hydroxy*-5-*methylphenyl*)*quinoxaline* (2 g.) as yellow, sublimable needles, m. p. 232° (Found : C, 57·0; H, 3·3; N, 8·6. $C_{15}H_{11}ON_2Br$ requires C, 57·1; H, 3·5; N, 8·9%). When refluxing was for only 30 min., a meriquinonoid compound was obtained, which crystallised as orange-red needles, m. p. 206°, from benzene, and underwent oxidation to the foregoing quinoxaline above its m. p.

Bromination of 2 : 4-*Dihydroxypropiophenone*.—The ketone (1 g.) in 50% aqueous acetic acid was treated with bromine (1 or 2 g.) in the usual way. 3 : 5-Dibromo-2 : 4-dihydroxypropiophenone formed colourless needles, m. p. 158°, from aqueous acetic acid (Found : Br, 49·6. Calc. for $C_9H_8O_3Br_2$: Br, 49·4%); Gnagy (*J. Amer. Chem. Soc.*, 1923, **45**, 807) gave m. p. 148°. The same compound was obtained by bromination in anhydrous acetic acid, and some α-bromo-compound, reacting with *o*-phenylenediamine, was detected, but no attempt was made to isolate it.

Bromination of 2-*Acetyl*-1-*naphthol*.—Reaction with 2 mols. of bromine in anhydrous acetic acid gave 4-bromo-2-bromoacetyl-1-naphthol (75%), m. p. 148°; Fries and Frellstedt (*loc. cit.*) gave m. p. 147°. Condensation of this ketone (2·25 g.) with *o*-phenylenediamine (0·7 g.) in the presence of sodium acetate (1 g.) gave 2-(4-*bromo*-1-*hydroxy*-2-*naphthyl*)*quinoxaline* (2 g.), ochre-yellow needles, m. p. 259° (decomp. >250°) (Found : C, 61·1; H, 3·2. $C_{18}H_{11}ON_2Br$ requires C, 61·5; H, 3·2%).

Bromination of 4-*Acetyl*-1-*naphthol*.—4-Acetyl-1-naphthol (5 g.; prepared by demethylation of 4-acetyl-1-methoxynaphthalene with pyridine hydrochloride) in anhydrous acetic acid (300 c.c.) with bromine (4·3 g.) gave the 2-*bromo-derivative* (5 g.), as colourless needles, m. p. 136° (from acetic acid) (Found : C, 54·0; H, 3·5. $C_{12}H_9O_2Br$ requires C, 54·3; H, 3·4%); the same compound was obtained by bromination in 50% aqueous acetic acid, and contained no labile bromine (aniline test).

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