Reactions of α-Halogeno-ketones with Aromatic Compounds. Part I. Reactions of Chloroacetone and 3-Chlorobutanone with Phenol and its Ethers.

By S. Husain Zaheer, Baldev Singh, Bharat Bhushan, P. M. Bhargava, I. K. Kacker, K. Ramachandran, V. D. N. Sastri, and N. Shanmukha Rao.

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Condensation of α-halogeno-ketones, R·CHCl·COR′ (R = H or Me; R′ = Me), with phenol or its ethers in the presence of concentrated sulphuric acid or aluminium chloride yielded substituted stilbene derivatives.

Condensation of chloroacetone with phenol and its ethers in presence of concentrated sulphuric acid and anhydrous aluminium chloride as catalysts has been studied with a view to prepare compounds, $CH_2Cl·CMeAr_2$, which might have insecticidal properties like those of DDT. Lippmann has reported (*Ber.*, 1912, **45**, 2490) that chloroacetone and phenol in the presence of hydrochloric acid at 100° give 1 : 2 : 2-tris-*p*-hydroxyphenylpropane. In our experiments, phenol reacted with chloroacetone in the presence of concentrated sulphuric acid at —10° to —5°, giving good yields of *trans*-4 : 4′-dihydroxy-α-methylstilbene, but at higher temperatures the reaction tended to be very vigorous, yielding dark sulphur-containing products. The diphenol and its diacetate and dimethyl ether were identical with the compounds synthesised earlier by Dodds *et al.* (*Proc. Roy. Soc.*, 1944, *B*, **132**, 83). Anisole and phenetole reacted similarly with chloroacetone, yielding 4 : 4′-dimethoxy- and 4 : 4′-diethoxy-α-methylstilbenes, which were also prepared by alkylation of the diphenol. The same three products were also obtained, although in lower yields, when chloroacetone was condensed with phenol, anisole, or phenetole in the presence of aluminium chloride at ~0°, with or without light petroleum as diluent.

When 3-chlorobutanone was used in place of chloroacetone, similar condensations occurred with phenol and anisole at 0°, yielding 2 : 3-di-*p*-hydroxyphenylbut-2-ene (characterised as its diacetyl derivative) and its dimethyl ether respectively, also obtained by Dodds *et al.* (*loc. cit.*).

In a preliminary note Bhargava and Zaheer (*Nature*, 1953, **171**, 746) postulated a reaction mechanism involving a Friedel–Crafts type of reaction as the first step. Sastri, Shanmukha Rao, and Zaheer (*Current Sci.*, 1953, **22**, 338), however, suggested a more probable reaction sequence, in which first the carbonyl group of the ketone reacts at the *p*-position of the aromatic compound, a subsequent rearrangement involving migration of one of the aromatic nuclei to the adjacent carbon atom and dehydrohalogenation.

Similar condensations with 2-chloropentan-3-one and 4-chlorohexan-3-one are being attempted with a view to synthesis of œstrogenic compounds.

EXPERIMENTAL

Phenol, anisole, and phenetole were freshly distilled before use. Chloroacetone (B.D.H.) was used as such. 3-Chlorobutanone was prepared by the chlorination of butanone (Korschun, *Ber.*, 1905, **38**, 1128).

4 : *4′-Dihydroxy-α-methylstilbene*.—(*a*) Concentrated sulphuric acid (29·4 g., 0·3 mole) was added dropwise during 1 hr. to a mechanically stirred mixture of phenol (56·4 g., 0·6 mole) and chloroacetone (27·75 g., 0·3 mole) cooled to about −10°, the stirring being continued for a further 2—3 hr. The orange-red pasty mass was treated with ice-cold water, a pale orange semi-solid product separating. This was washed with cold water and crystallised from hot aqueous alcohol. Pale orange crystals together with a small quantity of a colourless oil were obtained. The crystals which were collected and washed with a little light petroleum, had m. p. 115—120° (45 g.). Two recrystallisations from alcohol raised the m. p. to 176—179°; a further recrystallisation from benzene gave white shining plates, m. p. 182—183° (66·4%).

(*b*) A mixture of chloroacetone (4·6 g., 0·05 mole) and phenol (9·4 g., 0·1 mole) was added dropwise in 30—45 min. to a well-stirred suspension of anhydrous aluminium chloride (6·67 g., 0·05 mole) in light petroleum (b. p. 40—60°), cooled in an ice-bath. An orange-red sticky mass began to separate immediately, but stirring was continued for another 2 hr. Cold dilute hydrochloric acid was then added slowly and the upper fluorescent petroleum layer was separated, washed with water, dilute sodium hydrogen carbonate solution, and again with water, dried (Na_2SO_4), and evaporated. The sticky residue, twice crystallised from 25—30% alcohol, melted at 182—183° (3 g., 26·6%). The mother-liquor on concentration yielded a purple oil, which deposited some crystals during a long period.

The *diacetate*, prepared by acetyl chloride in pyridine at 0° and recrystallised from alcohol, formed plates, m. p. 123—124° (2·2 g. from 2·0 g.) (Found : C, 73·2; H, 6·1. $C_{19}H_{18}O_4$ requires C, 73·55; H, 5·8%). On hydrolysis with 15% aqueous potassium hydroxide, the diphenol was obtained in theoretical yield. The *dipropionate*, similarly prepared and crystallised, formed needles, m. p. 107—108° (2 g. from 2·4 g.) (Found : C, 75·0; H, 6·8. $C_{21}H_{22}O_4$ requires C, 74·6; H, 6·5%).

The diphenol (2·13 g.), methyl iodide (8·52 g.), anhydrous potassium carbonate (2·76 g.), and acetone (3·48 g.) were refluxed for 3—4 hr. After removal of acetone and excess of methyl iodide and treatment with water, a solid *dimethyl ether* was obtained, as plates (from alcohol), m. p. 124° (2·2 g.) (Found : C, 79·7; H, 7·3. $C_{17}H_{18}O_2$ requires C, 80·3; H, 7·1%); the *diethyl ether*, similarly prepared, formed needles, m. p. 105—106° (Found : C, 80·3; H, 8·0. $C_{19}H_{22}O_2$ requires C, 80·85; H, 7·8%), and the *di*-n-*propyl ether* formed plates, m. p. 107—108° (Found : C, 81·1; H, 8·8. $C_{21}H_{26}O_2$ requires C, 81·3; H, 8·4%), and the *diallyl ether*, similarly prepared but crystallised from acetone, formed plates, m. p. 94—95°, sparingly soluble in alcohol, benzene, and ethyl acetate (Found : C, 81·5; H, 7·5. $C_{21}H_{22}O_2$ requires C, 82·35; H, 7·2%).

4 : *4′-Dimethoxy-α-methylstilbene*.—(*a*) Concentrated sulphuric acid (9·8 g., 0·1 mole) was added dropwise during 0·5 hr. to a stirred mixture of anisole (16·2 g., 0·15 mole) and chloroacetone (6·9 g., 0·075 mole) at 0°, and the mixture was stirred for a further 4—5 hr. Water was then added, and the liquid which separated was extracted with ether. The extract was washed twice with water and dried ($CaCl_2$), and the ether removed. The resulting red viscous liquid was refluxed in hot alcohol for a few hours. Part of the alcohol was then distilled off and on cooling 4 : 4′-dimethoxy-α-methylstilbene crystallised (15 g., 77·5%). Recrystallised from hot alcohol it had m. p. and mixed m. p. with the above dimethyl ether, 124°.

(*b*) Reaction of chloroacetone (4·6 g., 0·05 mole) and anisole (10·8 g., 0·1 mole) in the presence of anhydrous aluminium chloride, as for the diphenol, yielded the dimethyl ether, m. p. and mixed m. p. 124°. The mother-liquor on prolonged refluxing and cooling yielded more of this compound (total yield 27·9%).

4 : 4′-Diethoxy-α-methylstilbene was similarly prepared from phenetole, chloroacetone, and sulphuric acid (yield, 59·4%); it had m. p. and mixed m. p. 105—106°. Use of aluminium chloride as catalyst gave a 18·5% yield.

2 : *3-Di*-p-*hydroxyphenylbut-2-ene*.—(*a*) Concentrated sulphuric acid (14·7 g., 0·15 mole) was added dropwise in 30 min. to a stirred mixture of phenol (9·4 g., 0·1 mole) and 3-chlorobutan-2-one

(5·3 g., 0·05 mole), stirring being continued for 2—3 hr. Treatment with ice-water and washing by decantation gave a dark red viscous mass, which was taken up in ether. The fluorescent ether layer was dried and the ether removed. The residual viscous liquid (10·2 g.) was steam-distilled to remove traces of phenol and taken up in ether, dried, and, after removal of ether, acetylated with acetic anhydride and sodium acetate. The oil obtained on addition of water was taken up in ether and after removal of ether, distilled under reduced pressure. The fraction coming over at 200—210°/2 mm. partly solidified. The crystals were filtered off, washed with cold ether–light petroleum, and twice recrystallised from alcohol. Colourless needles of 2 : 3-di-*p*-acetoxyphenylbut-2-ene (1·3 g., 8·0%), m. p. 123—124°, were obtained (Found : C, 74·3; H, 6·3. Calc. for $C_{20}H_{20}O_4$: C, 74·1; H, 6·2%). A mixed m. p. with an authentic specimen showed no depression.

The free diphenol was isolated only as an oil. When the reaction time was increased to 6—7 hr., and even when the quantity of sulphuric acid was reduced to one mol., only a semi-solid mass was obtained which, although it solidified when heated with ligroin (b. p. 80—100°), did not have a sharp m. p. and could not be purified.

(*b*) Anhydrous aluminium chloride (6·67 g., 0·05 mole) was added in small lots during 30 min. to a well-stirred, ice-cooled solution of phenol (9·4 g., 0·1 mole) and 3-chlorobutan-2-one (5·32 g., 0·05 mole) in dry light petroleum (100 ml.; b. p. 40—60°). A pink product, gradually deepening in colour to red, slowly separated. After another 3 hours' stirring, ice water (200 ml.) and a little dilute hydrochloric acid were added, followed by ether, which dissolved the reaction mass. The solvent layer was separated, washed successively with water, sodium hydrogen carbonate solution and water, dried (Na_2SO_4), and evaporated. The residue was steam-distilled and from the non-volatile portion, after washing with ether–light petroleum, a small quantity of solid melting at 194—196° was obtained, presumably the diphenol. The non-volatile residue on acetylation yielded the diacetate, m. p. and mixed m. p. with the earlier sample, 123—124°. With acetic anhydride in pyridine it gave a diacetate, m. p. 124° (from alcohol) alone or mixed with an authentic specimen.

2 : 3-*Di*-p-*methoxyphenylbut-2-ene*.—(*a*) Concentrated sulphuric acid (14·7 g., 0·15 mole) was added in 1 hr. to a stirred mixture of anisole (10·8 g., 0·1 mole) and 3-chlorobutanone (5·3 g., 0·05 mole) cooled in ice. After a further 4 hours' stirring, the dark-red semi-solid mass was treated with crushed ice and extracted with ether. The extract was washed with dilute sodium hydrogen carbonate solution and water, dried (Na_2SO_4), and evaporated. On distillation, a little unchanged anisole (0·5 g.) came over first, followed by the main fraction, b. p. 190—200°/2 mm. This solidified on cooling in ice. Two crystallisations from light petroleum gave colourless needles, m. p. 129—130° (8 g., 59%) (Found : C, 80·0; H, 7·7; OMe, 22·4. Calc. for $C_{18}H_{20}O_2$: C, 80·6; H, 7·5; 2OMe, 23·2%). A mixed m. p. with an authentic sample prepared according to the procedure of Sisido, Nozaki, and Kurihara (*J. Amer. Chem. Soc.*, 1949, **71**, 2037) showed no depression.

Some experiments, yielded also an ether-insoluble substance which dissolved in benzene and was precipitated therefrom by light petroleum. This amorphous white powder, m. p. 180—190°, contained sulphur and was not investigated further. Reaction at 25—30° gave a dark viscous mass from which no solid could be isolated.

(*b*) A cooled mixture of anisole (10·8 g., 0·10 mole) and 3-chlorobutan-2-one (5·3 g., 0·05 mole) was added dropwise in 1 hr. with stirring to anhydrous aluminium chloride (13·35 g., 0·1 mole) cooled in ice–salt. After 5 hours' stirring, the dark-red solid mass was decomposed with crushed ice and dilute hydrochloric acid and extracted with ether. The extract was washed with dilute hydrochloric acid, followed by dilute sodium hydrogen carbonate solution and distilled water, and dried (Na_2SO_4). The solvent was distilled off and the residue distilled under reduced pressure. Unchanged anisole (0·5 g.) distilled first and then 5·5 g. of a product of b. p. 180—200°/2 mm., which solidified partly and yielded 2 g. of colourless needles. After two crystallisations from light petroleum, it had m. p. and mixed m. p. with the previous sample, 130—131° (yield 41%).

Demethylation. To the Grignard reagent from 2 g. of magnesium and 12 g. of methyl iodide was added a solution of 2 g. of the last compound in 30 ml. of ether. The solvent was removed and the residue heated at about 170° for 40 min. On working up in the usual way, colourless prisms of 2 : 3-di-*p*-hydroxyphenylbut-2-ene, m. p. 194—195°, were obtained.

Central Laboratories for Scientific and Industrial Research,
Hyderabad-Deccan, 7, India.
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