

Reactions of α -Halogeno-ketones with Aromatic Compounds. Part II.
Reactions of 2-Chloropentan-3-one, 4-Chlorohexan-3-one, and s-Di-
chloroacetone with Phenol and its Ethers.*

By S. HUSAIN ZAHEER, BALDEV SINGH, BHARAT BHUSHAN, I. K. KACKER,
K. RAMACHANDRAN, and N. SHANMUKHA RAO.

[Reprint Order No. 6011.]

Condensation of 2-chloropentan-3-one and 4-chlorohexan-3-one with anisole in the presence of sulphuric acid or aluminium chloride yielded the triaryl-pentane and -hexane respectively, and compounds of the type $\text{CAr}_2\text{:CAlk}_2$, but no stilbene derivatives. *s*-Dichloroacetone condensed with phenol and its ethers to yield 1 : 3-dichloro-2 : 2-di-*p*-hydroxyphenylpropane and the corresponding ethers. With aluminium chloride resins resulted. None of these products had marked insecticidal action.

CONDENSATION of chloroacetone and 3-chlorobutanone with phenol and its ethers in the presence of concentrated sulphuric acid or anhydrous aluminium chloride, yielded substituted stilbene derivatives (Part I*). It was hoped that this condensation could be extended to other α -halogeno-ketones, leading to a simpler synthesis of oestrogenic compounds, *e.g.*, "diethylstilbæstrol," by use of 4-chlorohexan-3-one. However, we failed to obtain stilbene derivatives when 2-chloropentan-3-one or 4-chlorohexan-3-one condensed with phenol or anisole under the conditions described earlier or modifications thereof: instead, from anisole in the presence of aluminium chloride we obtained the olefins $\text{CAr}_2\text{:CMeEt}$ and $\text{CAr}_2\text{:CEt}_2$ respectively. With sulphuric acid, 2-chloropentan-3-one and anisole yielded 2 : 3 : 3-tri-*p*-methoxyphenylpentane, and 4-chlorohexan-3-one and anisole gave the olefin and 3 : 3 : 4-tri-*p*-methoxyphenylhexane. Similar reactions of these halogeno-ketones with phenol did not yield identifiable products, except that 2-chloropentan-3-one and phenol in the presence of sulphuric acid gave 2 : 3 : 3-tri-*p*-hydroxyphenylpentane.

It appears that in the above condensations the initial reaction at the carbonyl group (Sastri, Shanmukha Rao, and Zaheer, *Current Sci.*, 1953, **22**, 338) is followed by a rearrangement involving the migration of an alkyl group (instead of one of the aromatic nuclei) leading to compounds $\text{CAr}_2\text{:CAlk}_2$, and/or the reaction involves, in addition to the initial condensation of two aromatic nuclei at the carbonyl group, replacement of the chlorine on the adjacent carbon atom by another aromatic residue, leading to the triaryl products.

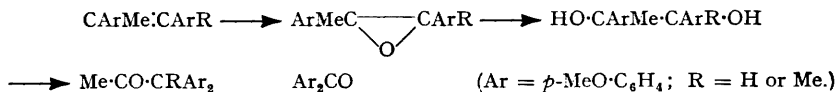
Similar condensations employing *s*-dichloroacetone were attempted as it was hoped that insecticidal compounds might be obtained. Bakeslar reported (U.S.P. 2,455,643/1948) the condensation of ketones or halogeno-ketones with arylalkyl compounds containing at least one nuclear hydrogen atom (*e.g.*, toluene, benzyl chloride) in the presence of sulphuric or phosphoric acids at 20–40°. Pinkston found (U.S.P. 2,551,050/1951) that *s*-dichloroacetone and ethylene dichloride react with aromatic hydrocarbons having at least two replaceable nuclear hydrogen atoms, in the presence of Friedel-Crafts catalysts at 60–115°, yielding resins. In our experiments, chlorobenzene did not react with *s*-dichloroacetone in presence of concentrated sulphuric acid at 0° or at room temperature (29°). Condensation with phenol at 0–5° yielded 1 : 3-dichloro-2 : 2-di-*p*-hydroxyphenylpropane, and anisole and phenetole similarly gave 1 : 3-dichloro-2 : 2-di-*p*-methoxy- and -di-*p*-ethoxy-phenylpropane respectively. In the presence of anhydrous aluminium chloride, in place of sulphuric acid, *s*-dichloroacetone gave only resins.

None of these compounds showed marked insecticidal action against *Bruchus chinensis*, L.

During the identification of these products, it was found that, although 4 : 4'-dimethoxy- α -methylstilbene and 2 : 3-di-*p*-methoxyphenylbut-2-ene on oxidation with permanganate

* Part I, *J.*, 1954, 3360.

yielded, as expected, *p*-anisic acid and *p*-methoxyphenyl methyl ketone respectively, both yielded in addition di-*p*-methoxyphenyl ketone on oxidation with chromic acid in acetic acid. This may be explained on the assumption that an epoxide is first formed (Byers and Hickinbottom, *J.*, 1948, 1334; Hickinbottom and Wood, *Nature*, 1951, **168**, 34), yielding a glycol on hydration, which by a pinacole-pinacolone type rearrangement, followed by further oxidation gives the ketone:



Compounds of the type $\text{CAr}_2\text{:CAlk}_2$ gave di-*p*-methoxyphenyl ketone on oxidation with either permanganate or chromic acid.

EXPERIMENTAL

Phenol, anisole, and phenetole were freshly distilled before use.

4-Chlorohexan-3-one.—Attempts to prepare this compound from 4-hydroxyhexan-3-one and thionyl chloride proved unsuccessful. α -Chloro-*n*-butyryl chloride and diethylcadmium gave very poor yields of the desired compound (b. p. 50–54°/17 mm.), the major product being a liquid, b. p. 105–108°/17 mm. The chlorohexanone was obtained by chlorination of hexan-3-one, which was prepared by treating *n*-butyryl chloride with diethylcadmium (yield 46%; cf. Gilman and Nelson, *Rec. Trav. chim.*, 1936, **55**, 518) or, more conveniently, pyrolysis of an equimolar mixture of propionic and butyric acid with manganous oxide as catalyst (Cowan, Jeffrey, and Vogel, *J.*, 1940, 171). A mixture of chlorine and carbon dioxide was bubbled through hexan-3-one, cooled in ice, the exit gases being bubbled through a weighed quantity of distilled water. When the total increase in weight was about 65% of the weight of the ketone taken, chlorination was stopped, and the product washed with water, dried (Na_2SO_4), and fractionally distilled in a Griener column under reduced pressure. From 340 g. of chlorinated hexan-3-one, after three fractionations, were obtained 193 g. of 4-chlorohexan-3-one (b. p. 49°/15 mm., 152.5–153°/712 mm.) (Blaise, *Compt. rend.*, 1912, **155**, 49, gives 53.5°/17 mm.), 40 g. of hexan-3-one, 35 g. of a chloro-ketone (b. p. 61–65°/15 mm., 170–172°/712 mm., possibly 2-chlorohexan-3-one), and 28 g. of another chloro-ketone (b. p. 72–75°/15 mm., 182–184°/712 mm.). 4-Chlorohexan-3-one was identified by oxidation with nitric acid (Van Raymenant, *Bull. Acad. roy. Belg.*, 1900, 724) to α -chlorobutyric acid, b. p. 100–102°/15 mm., d_4^{25} 1.19, n_D^{25} 1.439 (*p*-toluidide, m. p. 98°). The following derivatives of 4-chlorohexan-3-one were prepared: 2:4-dinitrophenylhydrazone, m. p. 64–65°; 2:4-dinitrophenylosazone, m. p. 259–260°; semicarbazone, m. p. 254°; phenylosazone, m. p. 137°.

Reaction of 2-Chloropentan-3-one and Anisole.—(a) Concentrated sulphuric acid (9.8 g., 0.1 mole) was added dropwise during 1 hr. to a stirred mixture of anisole (8.7 g., 0.08 mole) and 2-chloropentan-3-one (5 g., 0.04 mole) at 0°, stirring being continued for a further 5 hr. The red mass was kept overnight at 5–10°, treated with ice-cold water, and taken up in ether. The extract was washed with water, dilute sodium hydrogen carbonate solution, and again with water, then dried (Na_2SO_4), and the ether removed. The residue was distilled, unchanged reactants coming over first (5.2 g., b. p. 40–44°/2 mm.), followed by 2:3:3-*tri-p*-methoxyphenylpentane (4.2 g.), b. p. 160–180°/2 mm., which partly solidified. After two crystallisations from light petroleum, this had m. p. 142–143° (Found: C, 80.2; H, 6.7. $\text{C}_{26}\text{H}_{30}\text{O}_3$ requires C, 80.0; H, 7.7%).

(b) A cooled mixture of anisole (8.7 g.) and 2-chloropentan-3-one (5 g.) was added dropwise in 1 hr. with stirring to anhydrous aluminium chloride (10.7 g., 0.08 mole) cooled in an ice-bath. A dark red mass gradually becoming viscous was formed as stirring was continued for another 5 hr. Crushed ice and dilute hydrochloric acid were then added, followed by ether. The ether extract was washed with dilute hydrochloric acid, then dilute sodium hydrogen carbonate solution and water, and dried (Na_2SO_4). The solvent was distilled off and the residue (11.4 g.) distilled, yielding unchanged starting material (2.25 g.), 1:1-di-*p*-methoxyphenyl-2-methylbut-1-ene as a pale yellow oil (5.7 g.; b. p. 168–172°/2 mm.), and a residue (2.4 g.). During several months at 0° the oil partly crystallised. After two crystallisations from alcohol, it had m. p. 83–84° (Found: C, 80.8; H, 7.9. Calc. for $\text{C}_{19}\text{H}_{22}\text{O}_2$: C, 80.9; H, 7.8%). On oxidation with permanganate or chromic acid in acetic acid, it yielded di-*p*-methoxyphenyl ketone, m. p. and mixed m. p. 144–145° (2:4-dinitrophenylhydrazone, m. p. 185–187°).

Reaction of 2-Chloropentan-3-one with Phenol.—2-Chloropentan-3-one (5 g., 0.04 mole) and phenol (7.5 g., 0.08 mole) in concentrated sulphuric acid (9.8 g., 0.1 mole) at 0° gave a red viscous mass. After 5 hr. this was treated with ice and extracted with ether. The ether extract, washed with dilute sodium hydrogen carbonate solution and water, was dried (Na₂SO₄) and the ether removed. The residue was methylated with methyl sulphate and sodium hydroxide and the product (5.3 g.) was distilled, giving anisole (2 g.) followed by a fraction (2.5 g.), b. p. 140—200°/2 mm. This gradually deposited crystals, which after two crystallisations from alcohol had m. p. 141—142° alone or mixed with 2 : 3 : 3-tri-*p*-methoxyphenylpentane.

Reaction at room temperature gave a similar result.

Reaction of 4-Chlorohexan-3-one with Anisole.—(a) Concentrated sulphuric acid (14.7 g., 0.15 mole), anisole (10.8 g., 0.1 mole), and 4-chlorohexan-3-one (6.8 g., 0.05 mole) at 0°, reacting as in (a) above, gave unchanged reactants (8 g.; b. p. 42—43°/2 mm.), and an oil (3.5 g.; b. p. 170—180°/2 mm.), which deposited colourless needles (0.3 g.) of 3 : 3 : 4-tri-*p*-methoxyphenylhexane. Crystallised twice from light petroleum this had m. p. 142—143° (Found : C, 80.1; H, 7.1. C₂₇H₃₂O₃ requires C, 80.2; H, 7.9%). The rest of the distillate on prolonged storage in the refrigerator slowly deposited crystals (0.8 g.) of 2-ethyl-1 : 1-di-*p*-methoxyphenylbut-1-ene, m. p. 87—89° (cf. *J.*, 1940, 833) (Found : C, 81.2; H, 8.2. Calc. for C₂₆H₂₄O₂ : C, 81.1; H, 8.1%). This compound on oxidation with permanganate or chromic acid yielded di-*p*-methoxyphenyl ketone.

(b) A cooled mixture of anisole (16.2 g., 0.15 mole) and 4-chlorohexan-3-one (10.2 g., 0.075 mole) was added dropwise in 30 min. with stirring to anhydrous aluminium chloride (20 g., 0.15 mole) cooled in ice. After 3 hr. the dark red mass became too viscous for further stirring. It was kept for 8 hr. in ice and then decomposed with crushed ice and dilute hydrochloric acid and extracted with ether. Working up as above gave unchanged reactants (2 g.; b. p. 40—44°/2 mm.), an oil (12.6 g.; b. p. 160—180°/2 mm.), and a residue (7.2 g.). The oil during 4 days in a refrigerator with a little light petroleum deposited crystals (4.5g.) of the olefin which after two crystallisations from light petroleum had m. p. and mixed m. p. 87—89°.

Reaction of s-Dichloroacetone and Phenol.—Concentrated sulphuric acid (9.8 g., 0.1 mole) was added dropwise during 45 min. to a stirred mixture of phenol (9.4 g., 0.1 mole) and *s*-dichloroacetone (6.35 g., 0.05 mole) cooled in ice, the stirring being continued for a further 1 hr. A red solid mass was obtained. Crushed ice was then added, followed by ether. The ether extract was washed with dilute sodium hydrogen carbonate solution and water, and dried (Na₂SO₄), and ether removed. The residue was dissolved in benzene and kept overnight in the refrigerator. Light pink needles of 1 : 3-dichloro-2 : 2-di-*p*-hydroxyphenylpropane were obtained (13.2 g., 88.9%). Recrystallised from benzene, it showed no definite m. p. but darkened at 120° (Found : C, 61.0; H, 4.9; Cl, 22.9. C₁₅H₁₄O₂Cl₂ requires C, 60.6; H, 4.7; Cl, 23.9%). The diacetate, prepared by acetic anhydride in pyridine and recrystallised from alcohol, formed colourless needles, m. p. 149—150°. The ditoluene-*p*-sulphonate, prepared and recrystallised similarly, formed colourless plates, m. p. 118—119° (Found : C, 56.7; H, 4.3; Cl, 11.7; S, 10.4. C₂₉H₂₆O₆Cl₂S₂ requires C, 57.5; H, 4.3; Cl, 11.7; S, 10.6%).

The reactions of *s*-dichloroacetone with anisole and phenetole under similar conditions yielded 1 : 3-dichloro-2 : 2-di-*p*-methoxyphenyl-, m. p. 58—59° (Found : C, 62.9; H, 5.7; Cl, 22.4; OMe, 17.8. C₁₇H₁₈O₂Cl₂ requires C, 62.8; H, 5.5; Cl, 21.8; 2OMe, 19.1%), and -di-*p*-ethoxyphenyl-propane, m. p. 70—71° (Found : C, 64.5; H, 6.2; Cl, 21.1; OEt, 23.1. C₁₉H₂₂O₂Cl₂ requires C, 64.6; H, 6.2; Cl, 20.1; 2OEt, 25.5%).

Oxidation of 4 : 4'-Dimethoxy-α-methylstilbene.—(a) Potassium permanganate (1 g. in 25 ml. of water) and acetic acid (1 ml.) were added to 4 : 4'-dimethoxy-α-methylstilbene (0.5 g.), and the contents stirred for 1 hr. Excess of permanganate was decomposed (NaHSO₃) and from the filtrate anisic acid, m. p. 182—184°, was isolated by the usual methods.

(b) Chromic acid (4 g.), glacial acetic acid (20 ml.), and 4 : 4'-dimethoxy-α-methylstilbene (1 g.) were refluxed for 30 min. To the cooled mixture diluted with water, alkali was added to neutrality, followed by ether. The ether extract yielded di-*p*-methoxyphenyl ketone, m. p. and mixed m. p. 144—145°. The aqueous layer on acidification and ether extraction yielded anisic acid.

*Oxidation of 2 : 3-Di-*p*-methoxyphenylbut-2-ene.*—(a) The butene (0.5 g.) in acetone (25 ml.) was mixed with potassium permanganate (0.8 g. in 10 ml. water) and acetic acid (1 ml.). After 3 hr. the excess of permanganate was decomposed (NaHSO₃) and the filtrate made alkaline and extracted with ether. The ether extract yielded *p*-methoxyacetophenone (2 : 4-dinitrophenylhydrazone, m. p. and mixed m. p. 219—220°).

(b) Chromic acid (2 g.), glacial acetic acid (10 ml.), and the butene (0.5 g.) were refluxed for 30 min. Anisic acid, m. p. 180°, and the ketone, m. p. 144—145°, were obtained.

The authors acknowledge some preliminary work done by Dr. P. M. Bhargava. They are grateful to Dr. M. B. Naidu for carrying out the insecticidal tests.

CENTRAL LABORATORIES FOR SCIENTIFIC AND INDUSTRIAL RESEARCH,
HYDERABAD-DECCAN, 7, INDIA.

[Received, partly, December 14th, 1954;
partly, January 4th, 1955.]
