118. *Halogenated Ketones. Part V. Some Derivatives of ω-Chloroacetophenone.*

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The preparation of various amines, arsonic acids, and dichloroarsines of the ω-chloroacetophenone and the ω-chloroacetyldiphenyl series is described.

For the preparation of various amines related to ω-chloroacetophenone, required in connexion with investigations of their physiological properties, the corresponding nitro-compounds, many of which were known, appeared to be the most promising intermediates. It was clear, however, that most of the orthodox methods of reduction were unlikely to succeed on account of the labile nature of the halogen atom. It was also obvious, from a study of the properties of ω-chloro-*p*-aminoacetophenone, already described by Kunckell (*Ber.*, 1900, **33**, 2645), that the desired amino-compounds were likely to be unstable, except under carefully-controlled conditions. Fortunately, the method of reduction devised by Ruggli and Reichwein (*Helv. Chim. Acta*, 1937, **20**, 917) for the preparation of ω-chloro-*o*-aminoacetophenone from the corresponding nitro-compound, involving the use of copper bronze and warm concentrated sulphuric acid, proved to be generally applicable in this series. In this way *ω-chloro*-m-*amino*-, -p-*amino*-, -3 : 4-*diamino*- and -3 : 5-*diaminoacetophenones* were readily prepared, the *ω-chloro*-3 : 5-*dinitroacetophenone* being prepared by the action of diazomethane on the acid chloride. *ω-Chloro*-3-*amino*-4-*methoxyacetophenone* was obtained by hydrolysis of its N-*acetyl* derivative, the latter being prepared by the condensation of chloroacetyl chloride with acet-*o*-anisidide in the presence of aluminium chloride; oxidation to 3-acetamido-4-methoxybenzoic acid sufficed to prove its structure. Most of these amines of the chloroacetophenone series are devoid of lachrymatory properties but they produce marked sternutatory effects.

Fries and Finck (*Ber.*, 1908, **41**, 4277) described the rearrangement of the chloroacetyl derivative of *m*-cresol to ω-chloro-2-hydroxy-4-methylacetophenone. On repetition of this work it was found that *ω-chloro*-4-*hydroxy*-2-*methylacetophenone* was also formed in this reaction. The structure of the latter compound followed from its reduction with zinc dust in aqueous-alcoholic acetic acid to the known 4-hydroxy-2-methylacetophenone.

Gibson *et al.* (*Rec. Trav. chim.*, 1930, **49**, 1006) and Malinovskii (*J. Gen. Chem. Russia*, 1935, **5**, 1355; *Chem. Abs.*, 1941, **35**, 443) have shown that the application of the Friedel–Crafts reaction to aryldichloroarsines results in the replacement of the dichloroarsine group by an acyl group. Acylaryldichloroarsines had therefore to be prepared from the appropriate amino-ketones by means of the Bart reaction followed by chlorination and reduction of the arsonic acid. Following the procedure of Sergeev and Kudryashev (*J. Gen. Chem. Russia*, 1937,

7, 1488) for the *p*-isomeride, *m*-aminoacetophenone was converted into *m*-acetylphenylarsonic acid, the method being an improvement on that described by Gibson and Levin (*J.*, 1931, 2395). The acid was chlorinated in acetic acid solution and the m-*chloroacetylphenylarsonic* acid reduced to m-*chloroacetylphenyldichloroarsine* with sulphur dioxide in concentrated hydrochloric acid. *2-Amino-4'-acetyldiphenyl*, prepared by stannous chloride reduction of the corresponding nitro-compound, was converted similarly into *4'-acetyldiphenyl-2-arsonic acid* and *4'-chloroacetyldiphenyl-2-dichloroarsine*.

Experimental.

ω-Chloro-o-chloroacetamidoacetophenone.—A small quantity of the corresponding base (Ruggli and Reichwein, *loc. cit.*) was mixed with a few drops of chloroacetyl chloride, a drop of pyridine was added, and the mixture was warmed on the steam-bath for a few minutes. The product was poured into water, filtered off, washed with water, and crystallised from methanol. The *chloroacetyl* derivative formed long needles, m. p. 113° (Found : N, 5·8; Cl, 29·4. $C_{10}H_9O_2NCl_2$ requires N, 5·7; Cl, 28·8%).

ω-Chloro-m-aminoacetophenone.—*m*-Nitrophenacyl chloride (4·4 g.; Barkenbus and Clements, *J. Amer. Chem. Soc.*, 1934, **56**, 1369) dissolved in concentrated sulphuric acid (80 c.c.) was stirred and maintained at 40—50° while copper bronze (10 g.) was added in small portions during 30 minutes. The solution was diluted to 500 c.c. with water, and a solution of sodium hydroxide (120 g.) in water (300 c.c.) was added slowly with stirring and ice-cooling until the solution was faintly alkaline. The yellow precipitate was extracted with ether, and the ether solution dried and evaporated to dryness under reduced pressure. *ω-Chloro-m-aminoacetophenone* (2·8 g.) formed bright yellow needles, m. p. 90—91°, from ether (Found : N, 8·5; Cl, 20·8. C_8H_8ONCl requires N, 8·3; Cl, 20·9%). The base was readily soluble in dilute hydrochloric acid, and was rapidly decomposed by alkalis.

ω-Chloro-m-formamidoacetophenone.—ω-Chloro-*m*-aminoacetophenone (100 mg.) was heated on the steam-bath with anhydrous formic acid (1·5 c.c.) for 10 minutes, the red solution was poured into water, and the dried precipitate crystallised from chloroform. The *formyl* derivative formed buff-coloured needles, m. p. 135° (Found : N, 7·2. $C_9H_8O_2NCl$ requires N, 7·1%).

ω-Chloro-m-acetamidoacetophenone.—The base (100 mg.) was heated on the steam-bath with acetic anhydride, and the mixture poured into water. *ω-Chloro-m-acetamidoacetophenone* separated from aqueous acetic acid in fine needles, m. p. 128° (Found : N, 6·9; Cl, 16·6. $C_{10}H_{10}O_2NCl$ requires N, 6·6; Cl, 16·75%).

ω-Chloro-m-chloroacetamidoacetophenone.—A small quantity of the base was suspended in a slight excess of N-sodium hydroxide solution cooled in a freezing mixture. Chloroacetyl chloride was then added drop by drop, and the mixture well shaken after each addition, until it was apparent that excess had been added. The solid was filtered off, washed with water, and, on crystallisation from methyl alcohol, the *chloroacetyl* derivative formed clusters of buff-coloured needles, m. p. 110—111° (Found : N, 5·8; Cl, 29·5. $C_{10}H_9O_2NCl_2$ requires N, 5·7; Cl, 28·8%).

ω-Chloro-m-methylaminoacetophenone.—ω-Chloro-*m*-aminoacetophenone (1 g.) and dimethyl sulphate (0·8 g.) were mixed and gently warmed. A vigorous reaction took place with production of a brown viscous mass, which was cooled, dissolved in water, and the solution diluted to 100 c.c. The precipitated solid was extracted with ether, the ether dried (Na_2SO_4) and evaporated, and the residue crystallised first from methanol and then from aqueous methanol. *ω-Chloro-m-methylaminoacetophenone* formed long, pale yellow needles, m. p. 79—81° (Found : C, 59·1; H, 5·6; Cl, 19·0. $C_9H_{10}ONCl$ requires C, 58·9; H, 5·5; Cl, 19·3%). An ice-cold solution of the base in dilute hydrochloric acid yielded a white precipitate of the nitroso-compound on addition of sodium nitrite.

ω-Chloro-p-nitroacetophenone.—This was prepared as described by Ruggli and Reichwein (*loc. cit.*) for the *o*-isomer from 2·5 g. of *p*-nitrobenzoyl chloride. The product (2 g.) had m. p. 89°, which remained constant after successive crystallisations from alcohol, light petroleum (b. p. 40—60°), and alcohol–benzene (2 : 3). Drying at 80°/0·2 mm. for two hours and heating to 200° and cooling failed to raise the melting point. A specimen of highly-purified product, prepared by sublimation under diminished pressure, had m. p. 90° (Dale and Nierenstein, *Ber.*, 1927, **60**, 1026, give m. p. 107°) (Found : Cl, 17·7. Calc. for $C_8H_6O_3NCl$: Cl, 17·8%).

ω-Chloro-p-aminoacetophenone.—*p*-Nitrophenacyl chloride (500 mg.) was reduced as described above. In this case the solution obtained after filtration of the copper bronze was made faintly alkaline by cautious addition of sodium hydroxide before extraction with ether. The ketone (300 mg.) crystallised from aqueous methyl alcohol as flat yellow needles, m. p. 146°, undepressed on admixture with a specimen, m. p. 147°, prepared by the method of Kunckell (*loc. cit.*). The acetyl derivative had m. p. 210—211°, undepressed on admixture with an authentic specimen.

ω-Chloro-p-chloroacetamidoacetophenone was prepared similarly to the *ortho*-isomer; after two crystallisations from methyl alcohol it was obtained as straw-coloured needles, m. p. 170—171° (Found : N, 5·9; Cl, 28·9. $C_{10}H_9O_2NCl_2$ requires N, 5·7; Cl, 28·8%).

ω-Chloro-3 : 4-diaminoacetophenone.—ω-Chloro-3-nitro-4-aminoacetophenone (2 g.; Kunckell, *Ber. Dtsch. Pharm. Ges.*, 1911, **21**, 435; Jörlander, *Ber.*, 1917, **50**, 1458) was dissolved in concentrated sulphuric acid (40 c.c.) and reduced with copper bronze (5 g.) in the manner already described. The reaction mixture was poured on ice and the solution diluted with water to 400 c.c., heated to boiling, and filtered hot from the excess of copper bronze. The sparingly soluble sulphate of the diamine crystallised on cooling as small plates (1·7 g.) which rapidly darkened. The sulphate was decomposed by suspending in water (50 c.c.), covering with a layer of ethyl acetate (25 c.c.), and adding N-sodium hydroxide solution drop by drop with shaking until the aqueous layer was alkaline to bromothymol blue. The ethyl acetate layer was separated, washed with water, dried, and evaporated under reduced pressure. The residue was crystallised from chloroform giving *ω-chloro-3 : 4-diaminoacetophenone* (0·5 g.) in small red needles, m. p. 108° (decomp.). The diamine darkened in air and on heating in solvents (Found : N, 14·9; Cl, 18·9. $C_8H_9ON_2Cl$ requires N, 15·2; Cl, 19·2%).

ω-Chloro-3 : 5-dinitroacetophenone.—3 : 5-Dinitrobenzoyl chloride (8 g.) was dissolved in ether (200 c.c.; dried over sodium) and added in small portions to a solution of diazomethane (4·2 g.) in dry ether (200 c.c.) cooled to −5°. The solution rapidly became deep red and a sticky red solid was deposited on the walls of the vessel. After the addition was complete the solution was kept for an hour at −5°. Dry hydrogen chloride was then passed into the solution, first with ice cooling (15 minutes) and then at room temperature until the red solid had changed in colour to brown and effervescence had ceased. After being kept overnight the solution was filtered, and the filtrate evaporated to dryness under reduced pressure. The solid residues were combined and suspended in ethyl acetate (100 c.c.), and the suspension was shaken vigorously with sodium hydrogen carbonate solution (100 c.c.; 10%); the suspended solid dissolved and both layers were deep red. The mixture was filtered and the ethyl acetate layer separated, washed again with sodium hydrogen carbonate solution and then with water, dried, and evaporated. The dark red solid which remained was crystallised from chloroform (charcoal) yielding *ω-chloro-3 : 5-dinitroacetophenone* (3·5 g.) as yellow plates, m. p. 122° (Found: N, 11·5. $C_8H_5O_5N_2Cl$ requires N, 11·45%). The ketone reacted rapidly with hot sodium hydroxide solution to give a solution containing chloride ions and yielded 3 : 5-dinitrobenzoic acid on oxidation with potassium permanganate solution.

ω-Chloro-3 : 5-diaminoacetophenone.—The above ketone (1 g.) was dissolved in concentrated sulphuric acid (20 c.c.) and reduced with copper bronze (5 g.). The reaction mixture was filtered through a sintered glass plate and the white solid ($CuSO_4$) washed with concentrated sulphuric acid (5 c.c.). The filtrate was poured on ice and the solution, after dilution with water to 500 c.c., was cooled (ice), covered with a layer of ethyl acetate (100 c.c.), and stirred vigorously while sodium hydrogen carbonate (84 g.) was added in small portions until the acid had been neutralised. The ethyl acetate layer was separated, washed with water, dried, and evaporated under reduced pressure. The *base* crystallised from ethyl acetate–chloroform (1 : 1) in the form of yellowish-brown silky needles (500 mg.), decomp. 115° (Found: N, 15·0; Cl, 19·3. $C_8H_9ON_2Cl$ requires N, 15·2; Cl, 19·2%). The *diacetyl* derivative crystallised from ethyl alcohol in lustrous flat needles, m. p. 222° (decomp.) (Found: N, 10·2; Cl, 13·3. $C_{12}H_{13}O_3N_2Cl$ requires N, 10·4; Cl, 13·2%).

ω-Chloro-3-acetamido-4-methoxyacetophenone.—Acet-*o*-anisidide (10 g.), chloroacetyl chloride (20 g.), and carbon disulphide (50 c.c.) were mixed and vigorously stirred in a flask fitted with a reflux condenser. Aluminium chloride (30 g.) was then added in 6 equal portions at 3 minute intervals; a brisk reaction took place with separation of a violet-red oil. After being stirred for a further 15 minutes the reaction was completed by being heated on the steam-bath for 15 minutes. The reaction mixture was cooled, the carbon disulphide decanted, and the residual oil decomposed with ice and dilute hydrochloric acid, leaving a buff-coloured solid which was filtered off and washed well with water. After repeated crystallisation from acetic acid the *ω-chloro-3-acetamido-4-methoxyacetophenone* (11 g.) was obtained as needles, m. p. 185—186° (softening at 180°) (Found: N, 6·1; Cl, 15·5. $C_{11}H_{12}O_3NCl$ requires N, 5·8; Cl, 14·7%). The substance was not soluble in cold sodium hydroxide solution and gave no coloration with alcoholic ferric chloride.

The above acetyl compound (200 mg.) was shaken for one hour at room temperature with sodium hypobromite solution (1·2 g. of bromine added to 30 c.c. of N-sodium hydroxide cooled in ice), then filtered from solid matter and cooled while excess of sulphur dioxide was bubbled into the solution. 3-Acetamido-4-methoxybenzoic acid (110 mg.) was deposited as fine needles, m. p. 226°. The acid was recrystallised from alcohol forming iridescent plates, m. p. 266—267° (decomp.), undepressed on admixture with an authentic specimen of the acid (Simonsen and Rau, *loc. cit.*).

ω-Chloro-3-amino-4-methoxyacetophenone.—The above acetyl compound (1 g.) was heated under reflux with a mixture of hydrochloric acid (8 c.c.) and water (16 c.c.) until solution was complete (about 10 minutes); after cooling, crystals of the hydrochloride of the base were deposited. This cold solution was covered with a layer of ethyl acetate (25 c.c.), and excess of sodium hydrogen carbonate added with stirring. The ethyl acetate layer was separated, washed with water, dried, and evaporated under reduced pressure. *ω-Chloro-3-amino-4-methoxyacetophenone* (650 mg.) crystallised from methanol in almost colourless lustrous plates, m. p. 114° (Found: N, 7·3; Cl, 181. $C_9H_{10}O_2NCl$ requires N, 7·0; Cl, 17·8%). The base decomposed into a brown insoluble substance on prolonged heating in a vacuum at 80°.

ω-Chloro-4-hydroxy-2-methylacetophenone.—*m*-Cresol (21·6 g.) was treated as described by Fries and Finck (*loc. cit.*), and the crude product distilled with superheated steam at 200°. The product (4·5 g.) which separated from the distillate was extracted with light petroleum (b. p. 40—60°). The soluble fraction, after crystallisation from the same solvent and then from water, formed needles, m. p. 100°, of ω-chloro-2-hydroxy-4-methylacetophenone. Repeated crystallisation of the insoluble fraction from benzene gave *ω-chloro-4-hydroxy-2-methylacetophenone* as needles, m. p. 147·5° (Found: C, 58·2; H, 4·7. $C_9H_9O_2Cl$ requires C, 58·55; H, 4·9%). On reduction with zinc dust in aqueous-alcoholic acetic acid (Stephen and Weizmann, *J.*, 1914, **105**, 1046) 4-hydroxy-2-methylacetophenone, m. p. 128° (cf. Nencki and Stoeber, *Ber.*, 1897, **30**, 1770, and Eijkmann, *Chem. Zentr.*, 1904, I, 1597), was obtained.

m-*Chloroacetylphenylarsonic Acid.*—*m*-Aminoacetophenone (13·5 g.) was converted into the arsonic acid (13 g.) as described by Sergeev and Kudryashev (*loc. cit.*) for the *p*-isomeride. A solution of chlorine (1·5 g.) and the arsonic acid (5 g.) in glacial acetic acid (73 g.) was exposed to ultra-violet light for 3 hours, by which time the colour due to the chlorine had disappeared. Acetic acid was removed under reduced pressure, and dilution with water precipitated the crude m-*chloroacetylphenylarsonic acid* (2·2 g.), which crystallised from dilute acetic acid or hot water in needles, m. p. 202—203° (decomp.) (Found: Cl, 12·8. $C_8H_8O_4ClAs$ requires Cl, 12·7%). The acid had similar properties to those of the *p*-isomeride.

m-*Chloroacetylphenyldichloroarsine.*—A mixture of the arsonic acid (2 g.) and concentrated hydrochloric acid (10 c.c.), to which a crystal of potassium iodide had been added, was heated on the steam-bath, and a stream of sulphur dioxide was passed in until the aqueous layer became transparent (1½ hours). The heavy oil (1·85 g.) was removed with benzene and distilled yielding m-*chloroacetylphenyldichloroarsine* as a pale yellow, viscous, oil, b. p. 170—180°/0·8 mm., $n_D^{21\cdot5°}$ 1·6302 (Found: C, 32·3; H, 1·9; Cl, 35·3. $C_8H_6OCl_3As$ requires C, 32·1; H, 2·0; Cl, 35·5%).

4'-Acetyldiphenyl-2-arsonic Acid.—2-Nitro-4'-acetyldiphenyl was prepared from 2-nitrodiphenyl by means of the Friedel–Crafts reaction, as described by Grieve and Hey (*J.*, 1933, 971). Reduction of the nitro-compound (18 g.) with stannous chloride gave *2-amino-4'-acetyldiphenyl* (8·6 g.) which crystallised from dilute methanol in yellow plates, m. p. 88—90° (Found : C, 79·4; H, 6·2; N, 6·4. $C_{14}H_{13}ON$ requires C, 79·6; H, 6·2; N, 6·6%). The amine (8·6 g.) was dissolved in methyl alcohol (60 c.c.), and concentrated sulphuric acid (5 g.) was added. After addition of arsenic trichloride (12·9 g.) the mixture was diazotised with aqueous sodium nitrite (3·5 g. in 5 c.c.). Subsequently cuprous chloride (0·5 g.) was added and the solution kept overnight. Boiling water (50 c.c.) was added, and the precipitated arsonic acid filtered off from the cold mixture. The crude semi-solid acid was triturated with acetone to remove gummy impurities. On crystallisation from methanol *4'-acetyldiphenyl-2-arsonic acid* separated in pale yellow needles, m. p. 235—236° with previous softening (Found : C, 52·0; H, 4·6. $C_{14}H_{13}O_4As$ requires C, 52·5; H, 4·1%).

4'-Chloroacetyldiphenyl-2-dichloroarsine.—The arsonic acid (3·09 g.) was chlorinated in glacial acetic acid solution, as described for *m*-acetylphenylarsonic acid, giving *4'-chloroacetyldiphenyl-2-arsonic acid* (2·2 g.) which crystallised from acetic acid in needles, m. p. 205—206° (Found : Cl, 12·3. $C_{14}H_{12}O_4ClAs$ requires Cl, 10·0%). Analysis showed that the acid was not pure but the impurities were successfully removed during the reduction stage. The arsonic acid (1·9 g.) was treated with sulphur dioxide as before, except that alcoholic hydrogen chloride replaced the concentrated hydrochloric acid previously used. In this manner *4'-chloroacetyldiphenyl-2-dichloroarsine* (1·3 g.) was obtained, which separated from alcohol in yellow needles, m. p. 105—106° (Found : C, 44·9; H, 2·9; Cl, 28·5. $C_{14}H_{10}OCl_3As$ requires C, 44·8; H, 2·7; Cl, 28·3%).

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