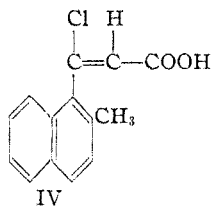
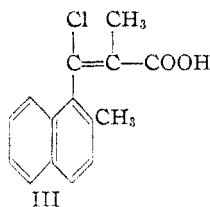
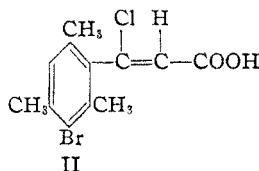
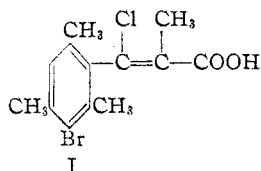


[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

# Restricted Rotation in Aryl Olefins. IV. Preparation and Resolution of $\beta$ -Chloro- $\beta$ -(2-methoxy-4,6-dimethyl-5-chlorophenyl)- $\alpha$ -methylacrylic and the Corresponding Acrylic Acid

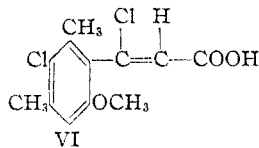
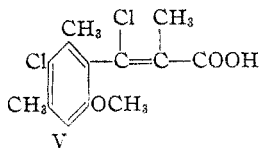
BY ROGER ADAMS AND W. J. GROSS<sup>1</sup>

The molecules shown by formulas I, II, III and IV and a few of their derivatives have been resolved and the active forms shown to be very resistant to racemization. The half-life periods in boiling *n*-butanol are for I, no racemization; for II, two hundred minutes; for III, seventy hours; for IV, seventy minutes. These values show semi-



quantitatively the relative interference effects of the hydrogen and methyl on the  $\alpha$ -carbon to the carboxyl (compare I and II; also III and IV) and of the *ortho* methyl and  $-\text{CH}=\text{C}-$  group in the aromatic nucleus (compare I and III; also II and IV).

Analogous derivatives to compounds I and II have now been synthesized and resolved in which an *ortho* methyl group in the benzene ring has been substituted by the smaller methoxyl group (V and VI).



The active forms of these molecules racemized so rapidly in boiling *n*-butanol that quantitative racemization measurements were impossible under these conditions. The active form of compound V was consequently racemized in *n*-butanol at 44° and the half-life determined as one hundred and seventy-three minutes; the active form of com-

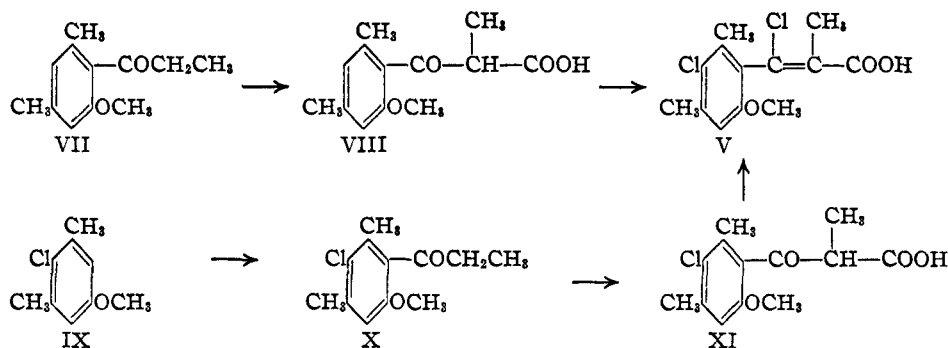
pound VI had a half-life period of about nine minutes in *n*-butanol at 20°. Although the racemization values of compounds I, II, III and IV taken in boiling *n*-butanol cannot be compared quantitatively with those of compounds V and VI taken at other temperatures, the relative ease of racemization of the latter two is striking. It demonstrates forcibly the enormous difference in the interference effects of the methoxyl and methyl groups in the ring and again of the methyl and hydrogen on the  $\alpha$ -carbon to the carboxyl. The alkaloidal salts of acids V and VI were obtained in only one form though mutarotation was not observed at room temperature.

No attempt has been made to determine whether compounds V and VI have the carboxyl *cis* or *trans* to the side-chain chlorine. From considerations presented in the previous papers,<sup>1a, 1b</sup> the assumption is that the carboxyl is *trans*. A study of a model of compound VI indicates that only if the carboxyl is *trans* to the side-chain chlorine is interference possible.

The synthesis of compound V was effected in two ways. 1-Methoxy-3,5-dimethylbenzene was converted to 1-methoxy-3,5-dimethyl-2-propiophenone (VII) by means of propionic anhydride and aluminum chloride. Ethylmagnesium bromide followed by carbon dioxide gave  $\alpha$ -methyl-(2-methoxy-4,6-dimethylbenzoyl)-acetic acid (VIII). The yield was only 40% and an unidentified by-product was obtained which probably originated from the action of the Grignard reagent on the keto form of the propiophenone. Since completely hindered ketones usually react entirely in the enol form with the Grignard reagent, the large by-product may be indicative of the decreased interference present as compared with that in the mesitylene analogs.

The usual procedure for obtaining the desired  $\beta$ -chloro-acrylic acid from the keto acid is by the use of phosphorus pentachloride in phosphorus oxychloride. In this instance, however, chlorination of the ring took place at the same time giving a mixture from which two compounds were isolated, one postulated as having structure V and

(1) For previous papers see (a) Adams and Miller, *THIS JOURNAL*, **62**, 53 (1940); (b) Adams, Anderson and Miller, *ibid.*, **63**, 1589 (1941); (c) Adams and Binder, *ibid.*, **63**, 2773 (1941).



the other with no chlorine in the ring. The position of the chlorine in the ring in V was determined by preparing 1-methoxy-3,5-dimethyl-4-chlorobenzene (IX) and converting it to the 1-methoxy-3,5-dimethyl-4-chloro-2-propionophenone (X). By following the same series of reactions through the keto acid (XI) as previously described, compound V was obtained. This latter method of preparation of V was distinctly superior to the former since the use of 1-methoxy-3,5-dimethyl-4-chlorobenzene as a raw material in place of 1-methoxy-3,5-dimethylbenzene served not only to prove the position of the chlorine in the ring but also permitted the formation of only one product in the final chlorination reaction.

The corresponding  $\beta$ -chloroacrylic acid (VI) was synthesized from 1-methoxy-3,5-dimethyl-4-chlorobenzene in a similar manner.

By starting with 1-ethoxy-3,5-dimethyl-4-chlorobenzene the 2-ethoxy derivatives corresponding to compounds V and VI were formed but no salts were found with suitable characteristics to make resolution studies possible.

### Experimental

**1-Methoxy-3,5-dimethyl-2-propionophenone.**—To a mechanically stirred mixture of 300 g. of carbon disulfide, 136 g. of 1-methoxy-3,5-dimethylbenzene<sup>2</sup> and 130 g. of propionic anhydride, was added 267 g. of anhydrous aluminum chloride at such a rate that the solvent refluxed gently. Upon completion of the addition a plastic mass formed making further stirring impossible. After the reaction mixture had stood for twelve hours the solvent was decanted and the residue decomposed using iced hydrochloric acid. The oil which separated was extracted with ether, washed with aqueous sodium hydroxide and finally with dilute hydrochloric acid. Distillation gave a water-white liquid; b. p. 120–122° (2 mm.),  $n_D^{20}$  1.5160; yield 144 g. (75%).

*Anal.* Calcd. for  $C_{12}H_{16}O_2$ : C, 75.00; H, 8.40. Found: C, 75.46; H, 8.44.

Demethylation, observed in every experiment, increased

as the excess of aluminum chloride was increased. The yield reported is that obtained when minimum demethylation occurred.

**1-Hydroxy-3,5-dimethyl-2-propionophenone.**—Acidification of the sodium hydroxide washings obtained in the preparation of 1-methoxy-3,5-dimethyl-2-propionophenone gave 1-hydroxy-3,5-dimethyl-2-propionophenone. The crude product was recrystallized from a small amount of methanol, white crystals, m. p. 78° (cor.).

*Anal.* Calcd. for  $C_{12}H_{14}O_3$ : C, 74.11; H, 7.92. Found: C, 73.93; H, 7.98.

This substance was remethylated readily by dissolving it in the appropriate amount of aqueous sodium hydroxide and adding dropwise, with stirring, an excess of dimethyl sulfate. After heating the reaction mixture at 100° for one hour, it was cooled and extracted with ether. The ether extract was dried over anhydrous magnesium sulfate and then distilled to give 1-methoxy-3,5-dimethyl-2-propionophenone.

**$\alpha$ -Methyl-(2-methoxy-4,6-dimethylbenzoyl)-acetic Acid.**—A solution of 20 g. of 1-methoxy-3,5-dimethyl-2-propionophenone in 25 cc. of dry ether was added to 100 cc. of an ether solution containing slightly more than one mole equivalent of ethylmagnesium bromide. The mixture was refluxed for thirty minutes, then transferred to a catalytic hydrogenation apparatus, cooled in an ice-bath, and carbon dioxide<sup>3</sup> passed in at a pressure of 2–3 atm. After forty-five minutes the temperature was allowed to rise to that of the room and the addition of carbon dioxide continued for six hours.

The reaction mixture was then chilled in an ice-bath, and poured slowly into iced hydrochloric acid. The ether layer was extracted with aqueous sodium hydroxide and the aqueous extract immediately acidified with iced hydrochloric acid. The product was purified by dissolving it in an excess of petroleum ether (b. p. 60–110°) and concentrating by means of an air stream; white crystalline powder, m. p. 88–89° (cor.); yield 8 g. (30%). When pure the material is stable for several weeks.

*Anal.* Calcd. for  $C_{13}H_{18}O_4$ : C, 66.07; H, 6.82. Found: C, 66.57; H, 7.18.

Evaporation of the ether solution after extraction with aqueous sodium carbonate did not give the expected unreacted ketone but rather a substance of lower boiling point. This liquid, postulated as being a mixture of the tertiary alcohol and the corresponding dehydration product arising

(2) Rowe, Bannister, Seth and Storey, *J. Chem. Ind.*, **46T**, 469 (1930).

(3) Kohler and Baltzly, *THIS JOURNAL*, **54**, 4015 (1932); Fuson, Fugate and Fisher, *ibid.*, **61**, 2362 (1939).

from the normal Grignard addition reaction, was treated with acetic anhydride to effect complete dehydration. The purified product did not give the proper analysis, however, and no further investigation was attempted.

**$\beta$ -Chloro- $\beta$ -(2-methoxy-4,6-dimethylphenyl)- $\alpha$ -methylacrylic Acid.**—To a solution of 10 g. of  $\alpha$ -methyl-(2-methoxy-4,6-dimethylbenzoyl)-acetic acid in 50 cc. of ice cold phosphorus oxychloride, was added 25 g. of phosphorus pentachloride. After heating at 70° for one hour, the solution was poured onto 300 g. of ice. The product separated as an oil which solidified on standing. The crude material, after many careful fractional crystallizations from benzene, was shown to be a mixture of  $\beta$ -chloro- $\beta$ -(2-methoxy-4,6-dimethylphenyl)- $\alpha$ -methylacrylic acid and  $\beta$ -chloro- $\beta$ -(2-methoxy-4,6-dimethyl-5-chlorophenyl)- $\alpha$ -methylacrylic acid. Each was separated in a pure state but only in small amounts.  $\beta$ -Chloro- $\beta$ -(2-methoxy-4,6-dimethylphenyl)- $\alpha$ -methylacrylic acid was obtained from benzene as white crystals, m. p. 163–164° (cor.).

*Anal.* Calcd. for  $C_{13}H_{13}O_3Cl$ : C, 61.29; H, 5.89. Found: C, 61.15; H, 6.03.

$\beta$ -Chloro- $\beta$ -(2-methoxy-4,6-dimethyl-5-chlorophenyl)- $\alpha$ -methylacrylic acid was obtained from benzene as white crystals, m. p. 178–179° (cor.).

*Anal.* Calcd. for  $C_{13}H_{11}O_3Cl_2$ : C, 54.00; H, 4.88; neut. equiv., 289. Found: C, 54.43; H, 5.05; neut. equiv., 287.

**1-Methoxy-3,5-dimethyl-4-chlorobenzene (IX).**—A solution of 313 g. of 1-hydroxy-3,5-dimethyl-4-chlorobenzene<sup>4</sup> in 85 g. of sodium hydroxide dissolved in a small amount of water was stirred and to it was added dropwise an excess of dimethyl sulfate. After refluxing for two hours, the resulting oil was removed and the water layer extracted with ether. The oil and ether extracts were combined and dried by means of anhydrous magnesium sulfate, the ether was then removed and the residue distilled; b. p. 94–96° (6 mm.),  $n_D^{20}$  1.5365; yield 273 g. (80%).

*Anal.* Calcd. for  $C_9H_{11}OCl$ : C, 63.31; H, 5.91. Found: C, 64.09; H, 6.75.

**1-Methoxy-3,5-dimethyl-4-chloro-2-propiofenone (X).**—This product was prepared in a similar manner to 1-methoxy-3,5-dimethyl-2-propiofenone using 1-methoxy-3,5-dimethyl-4-chlorobenzene in place of 1-methoxy-3,5-dimethylbenzene. It was a white, crystalline solid, readily purified from petroleum ether (b. p. 60–110°), m. p. 66.5–67.5° (cor.); yield 125 g. (55%).

*Anal.* Calcd. for  $C_{12}H_{13}O_2Cl$ : C, 63.54; H, 6.66. Found: C, 64.01; H, 6.70.

Acidification of the sodium hydroxide washings gave 1-hydroxy-3,5-dimethyl-4-chloro-2-propiofenone, a white crystalline solid. This substance was not purified but was remethylated as described for the corresponding unchlorinated compound, 1-hydroxy-3,5-dimethyl-4-propiofenone.

Demethylation, observed in every experiment, increased as the excess of aluminum chloride was increased. The yield reported was that obtained when minimum demethylation occurred.

(4) Lesser and Gad, *Ber.*, **56B**, 974 (1923).

**$\alpha$ -Methyl-(2-methoxy-4,6-dimethyl-5-chlorobenzoyl)-acetic Acid (XI).**—A solution of 20 g. of 1-methoxy-3,5-dimethyl-4-chloro-2-propiofenone in 25 cc. of dry ether was added to 100 cc. of an ether solution containing slightly more than one mole equivalent of ethylmagnesium bromide. The mixture was refluxed for thirty minutes and carbonated as described for the corresponding unchlorinated propiofenone. The product was purified by crystallization from petroleum ether (b. p. 60–110°) and finally from benzene by dissolving it in an excess of the solvent and then concentrating; white crystalline powder, m. p. 118° (cor.); yield 12 g. (50%). When pure, the material was stable for several weeks. The crude product was satisfactory for conversion to  $\beta$ -chloro- $\beta$ -(2-methoxy-4,6-dimethyl-5-chlorophenyl)- $\alpha$ -methylacrylic acid.

*Anal.* Calcd. for  $C_{13}H_{13}O_4Cl$ : C, 57.76; H, 5.58. Found: C, 57.65; H, 5.61.

Evaporation of the ether solution after extraction with sodium carbonate yielded a liquid which was probably a mixture of the tertiary alcohol and the corresponding dehydration product, arising from the normal Grignard addition reaction to the keto form of the propiofenone.

**$\beta$ -Chloro- $\beta$ -(2-methoxy-4,6-dimethyl-5-chlorophenyl)- $\alpha$ -methylacrylic Acid (V).**—A sample of 10 g. of  $\alpha$ -methyl-(2-methoxy-4,6-dimethyl-5-chlorobenzoyl)-acetic acid was converted to the chloroacrylic acid derivatives by the procedure described for the corresponding unchlorinated phenyl derivative. It was purified by recrystallization first from petroleum ether (b. p. 60–110°) and then several times from benzene; white crystals, m. p. 178–179° (cor.); yield 5.5 g. (50%).

*Anal.* Calcd. for  $C_{13}H_{11}O_3Cl_2$ : C, 54.00; H, 4.88; neut. equiv., 289. Found: C, 54.00; H, 5.02; neut. equiv., 287.

**Resolution of  $\beta$ -Chloro- $\beta$ -(2-methoxy-4,6-dimethyl-5-chlorophenyl)- $\alpha$ -methylacrylic Acid (V).**—A solution of 2.7 g. of  $\beta$ -chloro- $\beta$ -(2-methoxy-4,6-dimethyl-5-chlorophenyl)- $\alpha$ -methylacrylic acid in 40 cc. of warm acetone was added to a solution of 2.9 g. of quinine in 40 cc. of warm acetone. After filtration the solution was allowed to stand for five days after which fraction A (2.5 g.) was removed. This was unchanged in rotation after recrystallization from acetone. The filtrate was then evaporated to 60 cc. and after standing two days fraction B (0.55 g.) was collected. Evaporation of the filtrate to 25 cc. yielded fraction C (1.2 g.) after standing four days. Evaporation to dryness gave fraction D. The rotations of fractions B and C were essentially identical with those of fraction A from which it was deduced that only one salt was obtained. No mutarotation was observed over a short period of time at room temperature.

*Anal.* Calcd. for  $C_{13}H_{13}O_3Cl_2N_2$ : C, 64.57; H, 6.24. Found: C, 64.68; H, 6.46. *Rotation.* (1*BdA*) 0.050 g. made up to 25 cc. with benzene at 20° gave  $\alpha_D$   $-0.12^\circ$ ; *l*, 2;  $[\alpha]_D^{20}$   $-30.0^\circ$ .

**$d$ - $\beta$ -Chloro- $\beta$ -(2-methoxy-4,6-dimethyl-5-chlorophenyl)- $\alpha$ -methylacrylic Acid.**—To a suspension of 2 g. of salt (fraction A) in 30 cc. of water was added 5 cc. of concentrated hydrochloric acid. After stirring at 5° for thirty minutes the product was filtered, washed with 5% hydrochloric acid and finally with water. The above was re-

peated until the product was quinine free; m. p. 177° (cor.).

*Rotation.* (*d*-acid) 0.100 g. made up to 25 cc. with *n*-butanol at 20° gave  $\alpha_D +0.18$ ; *l*, 2;  $[\alpha]^{20}_D +22.5^\circ$ .

**Racemization of *d*- $\beta$ -Chloro- $\beta$ -(2-methoxy-4,6-dimethyl-5-chlorophenyl)- $\alpha$ -methylacrylic Acid (V).**—A solution of 0.1 g. of the above *d*-acid in 25 cc. of *n*-butanol was placed in a polarimeter tube equipped with a water jacket through which was passed water at 44° from a constant temperature bath. The following  $\alpha_D$  values were obtained: at the start +0.18; after thirty minutes +0.16; after one hour +0.15; after one and a half hours +0.13; after two hours +0.11; after two and a half hours +0.09; after three and a half hours +0.07; after four and a half hours +0.06; after seven and a half hours +0.02. Calculated for a reversible unimolecular reaction, the half-life period is 173 minutes.

**1-Methoxy-3,5-dimethyl-4-chloro-2-acetophenone.**—To 300 g. of carbon disulfide, 171.5 g. of 1-methoxy-3,5-dimethyl-4-chlorobenzene and 102 g. of acetic anhydride, was added 267 g. of anhydrous aluminum chloride using exactly the same procedure employed to produce 1-methoxy-3,5-dimethyl-4-chloro-2-propiofenone. Distillation gave a white crystalline solid; b. p. 134–136° (3 mm.). It was purified by crystallization from dry ether, m. p. 76–77° (cor.); yield 127 g. (50%).

*Anal.* Calcd. for  $C_{11}H_{13}O_2Cl$ : C, 62.09; H, 6.16. Found: C, 61.92; H, 6.23.

As in the preparation of 1-methoxy-3,5-dimethyl-4-chloro-2-propiofenone, demethylation occurred. The product could be remethylated and purified readily, however, in exactly the same manner as the 1-hydroxy-3,5-dimethyl-4-chloro-2-propiofenone previously described.

**2-Methoxy-4,6-dimethyl-5-chlorobenzoyl Acetic Acid.**—A solution of 20 g. of 1-methoxy-3,5-dimethyl-4-chloro-2-acetophenone in 25 cc. of dry ether was added to 100 cc. of an ether solution containing slightly more than one mole equivalent of ethylmagnesium bromide. The bromomagnesium enolate precipitated and was carbonated in the same manner as 1-methoxy-3,5-dimethyl-4-chloro-2-propiofenone. Recrystallization of the crude product gave a white crystalline powder, m. p. 113° (cor.); yield 11 g. (45%).

*Anal.* Calcd. for  $C_{12}H_{13}O_4Cl$ : C, 56.11; H, 5.11. Found: C, 55.73; H, 5.24.

As in the case of  $\alpha$ -methyl-(2-methoxy-4,6-dimethyl-5-chlorobenzoyl)-acetic acid (XI), normal addition of the Grignard reagent apparently took place, for the main constituent of the residue was a liquid which was presumably the dehydrated tertiary alcohol.

**$\beta$ -Chloro- $\beta$ -(2-methoxy-4,6-dimethyl-5-chlorophenyl)-acrylic Acid (VI).**—To a solution of 10 g. of 2-methoxy-4,6-dimethyl-5-chlorobenzoyl acetic acid in 50 cc. of ice-cold phosphorus oxychloride was added 25 g. of phosphorus pentachloride. The mixture was heated in a water-bath at 70° for one hour, then poured onto 300 g. of ice. A solid separated and was purified by crystallization from petroleum ether (b. p. 60–110°) and finally from benzene; white crystals, m. p. 181–182° (cor.); yield 5.2 g. (48%).

*Anal.* Calcd. for  $C_{13}H_{12}O_3Cl_2$ : C, 52.34; H, 4.34. Found: C, 52.18; H, 4.49.

**Resolution of  $\beta$ -Chloro- $\beta$ -(2-methoxy-4,6-dimethyl-5-chlorophenyl)-acrylic Acid (VI).**—A solution of 6.3 g. of  $\beta$ -chloro- $\beta$ -(2-methoxy-4,6-dimethyl-5-chlorophenyl)-acrylic acid in 50 cc. of ethyl acetate was added to a solution of 7.5 g. of quinine in 70 cc. of ethyl acetate. After filtration the solution was evaporated to 40 cc. and at two-day intervals the crystals were filtered and 5 cc. of solvent was removed. The rotations of the various fractions thus obtained were essentially the same and the same *d*-acid was obtained from all fractions, indicating the formation of only one salt. The various fractions were unchanged in rotation after recrystallization from ethyl acetate. No mutarotation was observed over a short period of time at room temperature.

*Anal.* Calcd. for  $C_{13}H_{12}O_3N_2Cl_2$ : C, 64.05; H, 6.05. Found: C, 64.15; H, 6.22. *Rotation.* (l*BdA*) 0.050 g. made up to 25 cc. with benzene at 20° gave  $\alpha_D -0.10^\circ$ ; *l*, 2;  $[\alpha]^{20}_D -25.00^\circ$ .

***d*- $\beta$ -Chloro- $\beta$ -(2-methoxy-4,6-dimethyl-5-chlorophenyl)-acrylic Acid.**—To a suspension of 2 g. of salt in 30 cc. of water was added 5 cc. of concentrated hydrochloric acid. After stirring at 5° for thirty minutes the product was filtered and washed with 5% hydrochloric acid and finally with water. The above was repeated until the product was quinine free; m. p. 180° (cor.).

*Rotation.* (*d*-acid) 0.100 g. made up to 25 cc. with *n*-butanol at 20° gave  $\alpha_D 0.10^\circ$ ; *l*, 2;  $[\alpha]^{20}_D +12.5^\circ$ .

**Racemization of *d*- $\beta$ -Chloro- $\beta$ -(2-methoxy-4,6-dimethyl-5-chlorophenyl)-acrylic Acid (VI).**—A solution of 0.100 g. of the *d*-acid made up to 25 cc. with *n*-butanol at 20° gave the following values: at the start +0.10; after five minutes +0.08; after eight minutes +0.06; after fifteen minutes +0.04; after twenty minutes +0.02; after twenty-five minutes 0.00. Calculated for a reversible unimolecular reaction, the half-life period is approximately nine minutes.

**1-Ethoxy-3,5-dimethyl-4-chlorobenzene.**—This compound was prepared from 1-hydroxy-3,5-dimethyl-4-chlorobenzene in exactly the same manner as 1-methoxy-3,5-dimethyl-4-chlorobenzene was obtained from 1-hydroxy-3,5-dimethyl-4-chlorobenzene except that diethyl sulfate was used in place of dimethyl sulfate. The yield was 85%.

*Anal.* Calcd. for  $C_{10}H_{13}OCl$ : C, 65.00; H, 7.09. Found: C, 65.31; H, 7.15.

**1-Ethoxy-3,5-dimethyl-4-chloro-2-propiofenone.**—To 300 g. of carbon disulfide, 185 g. of 1-ethoxy-3,5-dimethyl-4-chlorobenzene and 130 g. of propionic anhydride was added 267 g. of anhydrous aluminum chloride using exactly the same procedure employed to produce 1-methoxy-3,5-dimethyl-4-chloro-2-propiofenone. It had a b. p. of 155–156° (7 mm.) and solidified to a crystalline mass which was purified from petroleum ether (b. p. 60–110°); white crystals, m. p. 53–54° (cor.); yield 123 g. (62%).

*Anal.* Calcd. for  $C_{13}H_{17}O_2Cl$ : C, 64.83; H, 7.10. Found: C, 64.77; H, 7.21.

As in the preparation of 1-methoxy-3,5-dimethyl-4-chloro-2-propiofenone deethylation occurred. However, the product could be reethylated and purified readily. The yield reported was that obtained when minimum deethylation occurred.

**$\alpha$ -Methyl-(2-ethoxy-4,6-dimethyl-5-chlorobenzoyl)-acetic Acid.**—A solution of 20 g. of 1-ethoxy-3,5-dimethyl-4-chloro-2-propiofenone was added to 100 cc. of an ether solution containing slightly more than one mole equivalent of ethylmagnesium bromide. The bromomagnesium enolate was insoluble and was carbonated in the same manner as the previously described bromomagnesium enolate of 1-methoxy-3,5-dimethyl-4-chloro-2-propiofenone. The crude product was recrystallized from dry ether; white crystalline powder turning yellow upon standing for twenty-four hours, m. p. 115.5–116.5° (cor.); yield 10 g. (41%).

*Anal.* Calcd. for  $C_{14}H_{17}O_4Cl$ : C, 59.02; H, 6.01. Found: C, 58.75; H, 5.95.

As in the preparation of  $\alpha$ -methyl-(2-methoxy-4,6-dimethyl-5-chlorobenzoyl)-acetic acid (XI), normal addition of the Grignard reagent to the keto form was observed. The main component of the residue was a liquid which boiled lower than the original ketone and was postulated as the corresponding dehydrated tertiary alcohol.

**$\beta$ -Chloro- $\beta$ -(2-ethoxy-4,6-dimethyl-5-chlorophenyl)- $\alpha$ -methylacrylic Acid.**—This compound was prepared in exactly the same manner as  $\beta$ -chloro- $\beta$ -(2-methoxy-4,6-dimethyl-5-chlorophenyl)- $\alpha$ -methylacrylic acid using  $\alpha$ -methyl-(2-ethoxy-4,6-dimethyl-5-chlorobenzoyl)-acetic acid as starting material. It formed faintly pink crystals from benzene, m. p. 141–142° (cor.); yield 6 g. (56%).

*Anal.* Calcd. for  $C_{14}H_{15}O_3Cl_2$ : C, 55.42; H, 5.31. Found: C, 55.41; H, 5.22.

**1-Ethoxy-3,5-dimethyl-4-chloro-2-acetophenone.**—To 300 g. of carbon disulfide, 185 g. of 1-ethoxy-3,5-dimethyl-4-chlorobenzene and 102 g. of acetic anhydride was added 267 g. of anhydrous aluminum chloride using the same procedure employed to produce 1-methoxy-3,5-dimethyl-4-chloro-2-propiofenone. It had a boiling point of 145–147° (7 mm.) and solidified on cooling to a crystalline mass which was purified by crystallization from petroleum ether (b. p. 60–110°); white crystals, m. p. 74° (cor.); yield 136 g. (60%).

*Anal.* Calcd. for  $C_{12}H_{13}O_2Cl$ : C, 63.54; H, 6.66. Found: C, 63.36; H, 6.73.

Deethylation occurred to a certain extent. However, the product from the aqueous sodium hydroxide extract could be reethylated.

The yield reported was that obtained when minimum deethylation occurred.

**2-Ethoxy-4,6-dimethyl-5-chlorobenzoylacetic Acid.**—A solution of 20 g. of 1-ethoxy-3,5-dimethyl-4-chloro-2-

acetophenone in 25 cc. of dry ether was added to 100 cc. of an ether solution containing slightly more than one mole equivalent of ethylmagnesium bromide. The bromomagnesium enolate precipitated and was carbonated in the same manner as 1-methoxy-3,5-dimethyl-4-chloro-2-propiofenone. Recrystallization of the crude product from dry ether gave a white crystalline powder, m. p. 103–104° (cor.); yield 13 g. (55%).

*Anal.* Calcd. for  $C_{13}H_{15}O_4Cl$ : C, 57.65; H, 5.88. Found: C, 57.65; H, 5.56.

The usual liquid by-product was observed, similar to that obtained in the carbonation experiments previously described.

**$\beta$ -Chloro- $\beta$ -(2-ethoxy-4,6-dimethyl-5-chlorophenyl)-acrylic Acid.**—This compound was prepared in exactly the same manner as  $\beta$ -chloro- $\beta$ -(2-methoxy-4,6-dimethyl-5-chlorophenyl)- $\alpha$ -methylacrylic acid using 2-ethoxy-4,6-dimethyl-5-chlorobenzoylacetic acid as starting material. It formed faintly pink crystals from benzene, m. p. 176–177° (cor.); yield 5.5 g. (51%).

*Anal.* Calcd. for  $C_{13}H_{14}O_3Cl_2$ : C, 53.96; H, 5.40. Found: C, 54.05; H, 5.01.

### Summary

1.  $\beta$ -Chloro- $\beta$ -(2-methoxy-4,6-dimethyl-5-chlorophenyl)-acrylic acid,  $\beta$ -chloro- $\beta$ -(2-methoxy-4,6-dimethyl-5-chlorophenyl)- $\alpha$ -methylacrylic acid,  $\beta$ -chloro- $\beta$ -(2-ethoxy-4,6-dimethyl-5-chlorophenyl)-acrylic acid, and  $\beta$ -chloro- $\beta$ -(2-ethoxy-4,6-dimethyl-5-chlorophenyl)- $\alpha$ -methylacrylic acid have been synthesized. The first two were resolved. The last two did not form salts suitable for resolution.

2. The active forms of the first two compounds had half-life periods, respectively, of nine minutes in *n*-butanol at 20° and one hundred and seventy-three minutes in *n*-butanol at 44°. This demonstrates the large increase in interference effected by substitution of the  $\alpha$ -hydrogen by an  $\alpha$ -methyl group. By comparison of these half-life periods with those of the previously described analogous mesitylene derivatives, the increased interference effect produced by an *ortho* methyl over an *ortho* methoxyl is exemplified once again.

URBANA, ILLINOIS

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