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

Restricted Rotation in Aryl Olefins. IX. Effect of Various Substituents on the Olefin Grouping[1]

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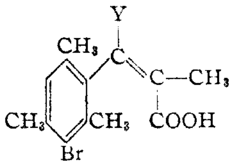
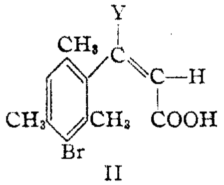
Molecules of the type shown in I and II have been under investigation and a comparison of the effect of different groups in the positions occupied by Y on the rate of racemization of the optical isomers has been made. Where Y is chlorine or bromine, all four molecules show high optical stability. The bromine causes greater restricted rotation than the chlorine and the methyl group *alpha* to the carboxyl in I induces greater stability than a hydrogen atom in the same position (II).

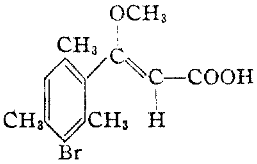


I

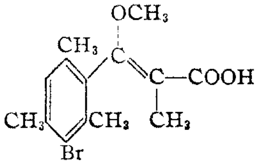


II

The corresponding molecules in which Y is methoxyl could not be resolved. The compound of type II with a hydrogen *alpha* to the carboxyl has been described previously.[1] Its non-resolvability was ascribed as being due, possibly, to the fact that the geometric configuration about the double bond might be represented by III and therefore different from that assumed to obtain in the molecules with the Y a halogen. According to models the restricted rotation in III would be much less than that in a molecule with the α-hydrogen and carboxyl interchanged. If this assumption were correct, resolution of a molecule with a methyl group *alpha* to the carboxyl as in IV would be expected. Since the molecule of this structure has now been synthesized and could not be resolved, it may be deduced that regardless of the orientation of the α-methyl and carboxyl groups, the methoxyl in the position held by Y in formula I or II is too small to permit restricted rotation. Whether these methoxyl-substituted molecules are of the geometric type III and IV or I and II cannot be concluded from the experimental facts.

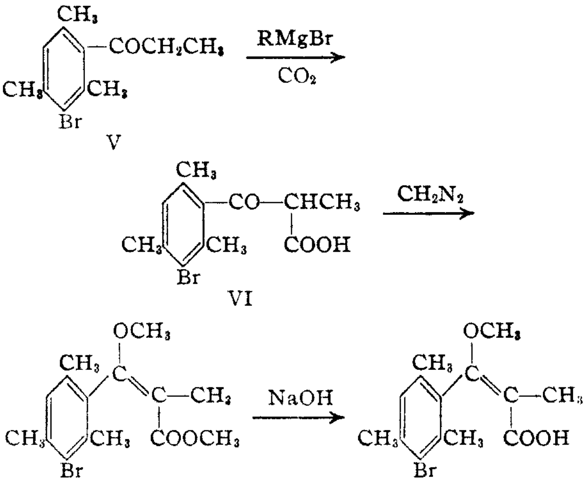


III



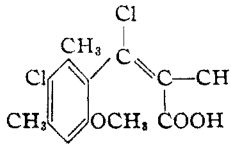
IV

Compound IV was synthesized from bromopropiomesitylene by the series of reactions[1] shown in V–VIII.

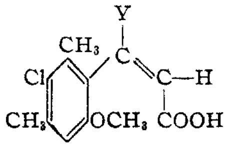


V VI VII VIII

Further study also has been made of molecules of type X, in which Y is bromine, iodine, methylthio and methoxyl. Molecule IX and that corresponding to X in which Y is chlorine have been made previously and both were resolved. The active forms are racemized readily; the former, however, is relatively much more stable.[3]

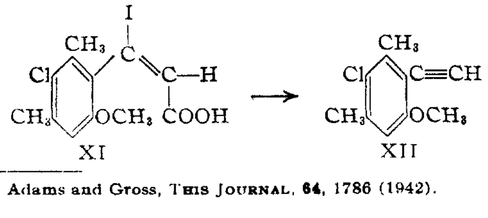


IX



X

The bromine compound was resolved and the active forms proved to have a half-life in n-butanol at 20° of four hundred and twenty minutes. This compares with nine minutes for the corresponding chlorine compound. Its stability is intermediate between that of the compounds of structure IX and X in which Y is chlorine. The alkaloidal salt was obtained in only one form although mutarotation was not observed at room temperature. The iodo compound XI could not be resolved since treatment with an alkaloid caused its immediate decomposition into the corresponding acetylene (XII) with loss of carbon dioxide and hydrogen iodide. Resolution of the methylthio and



XI XII

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[1] For previous paper see Adams and Theobald, THIS JOURNAL, 65, 2383 (1943).

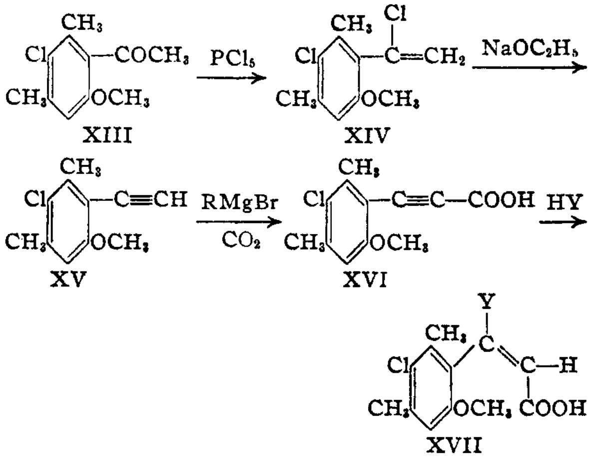
[2] An abstract of a thesis submitted in partial fulfillment of the requirements for the degree of Doctor of Philosophy in Chemistry.

[3] Adams and Gross, THIS JOURNAL, 64, 1786 (1942).

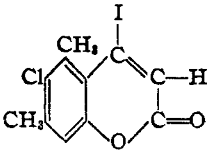
methoxyl derivatives also was unsuccessful but this was not unexpected since these groups are small as indicated by previous studies.

The published method for the synthesis of IX is different from that used in this investigation for the synthesis of compounds of formula X. The chlorine analog was therefore made by this second procedure and shown to be identical with that obtained in the earlier preparation.

The chlorine, bromine and iodine compounds were made by adding the appropriate halogen acid to the substituted propiolic acid as shown in XIII–XVII.[4] The methylthio derivative was produced by esterifying the propiolic acid (XVI) with diazomethane and adding methyl mercaptan. Saponification of the ester took place simultaneously with the addition. The methoxyl compound could not be made similarly by adding sodium methylate so its synthesis was accomplished from XIII by the series of reactions shown in V–VIII.



The bromine and iodine compounds corresponding to formula X were hydrolyzed. By refluxing the bromo or iodo derivatives with hydriodic acid in glacial acetic acid, the same coumarin was obtained, 4-iodo-5,7-dimethyl-6-chlorocoumarin (XVIII). By the action of refluxing



XVIII

hydrobromic acid in glacial acetic acid on the bromo compound, 4-bromo-5,7-dimethyl-6-chlorocoumarin resulted. The conditions of these hydrolyses were necessarily too vigorous to allow deductions concerning the configuration of the intermediate coumarinic acids.

Experimental

Methyl α-Methyl-β-methoxy-β-(2,4,6-trimethyl-3-bromophenyl)-acrylate (VII).—To an ether solution of the diazomethane generated from 11.5 g. of nitrosomethylurea was added gradually 8 g. of α-methyl-2,4,6-trimethyl-4-bromobenzoylacetic acid prepared according to the directions of Adams and Miller.[5] The flask was fitted with a stopper having a capillary outlet and was allowed to stand for forty-eight hours. At the end of this time, the solution was filtered and the ether removed by evaporation. The oil was purified by distillation under reduced pressure; fraction 1, b. p. 106–126° (2 mm.) consisted principally of crude keto ester, and solidified on standing; fraction 2, b. p. 127–140° (2 mm.), $n^{17}\text{D}$ 1.5618, was redistilled. The pure product had a b. p. 147–148° (4 mm.); $n^{17}\text{D}$ 1.5630; d_{20} 1.3110.

In most of the subsequent experiments, the oil was not purified, but was hydrolyzed directly to the acid.

Anal. Calcd. for $C_{15}H_{19}BrO_3$: C, 55.05; H, 5.86. Found: C, 55.04; H, 5.98.

If insufficient diazomethane was used or if the reaction mixture had not been allowed to stand for a sufficient length of time, the reaction product crystallized and proved to be chiefly methyl α-methyl-2,4,6-trimethyl-3-bromobenzoylacetate. After recrystallization from petroleum ether or ethanol, this material melted at 85–86° (cor.).

Anal. Calcd. for $C_{14}H_{17}BrO_3$: C, 53.68; H, 5.46. Found: C, 53.78; H, 5.68.

α-Methyl-β-methoxy-β-(2,4,6-trimethyl-3-bromophenyl)-acrylic Acid (VIII).—Crude methoxyacrylic ester prepared from 8.0 g. of the keto acid, was heated under reflux[6] on a steam-bath for thirty-six hours with a 20% ethanolic potassium hydroxide solution prepared by mixing 10 g. of potassium hydroxide with 7 cc. of water and 24 cc. of ethanol. At the end of this time, part of the ethanol was removed by distillation and the residue was poured into an excess of ice-water. The solution was neutralized with ice-cold sulfuric acid to a congo red end-point. The precipitated acid was separated by filtration and air-dried; yield, 5.5 g. (60%). The acid was recrystallized from a mixture of benzene and petroleum ether (b. p. 60–110°); m. p. 123–124° (cor.).

Anal. Calcd. for $C_{14}H_{17}BrO_3$: C, 53.68; H, 5.46. Found: C, 53.22; H, 5.42.

Attempted Resolution of α-Methyl-β-methoxy-β-(2,4,6-trimethyl-3-bromophenyl)-acrylic Acid.—A solution of 0.8369 g. of the acid in 5 cc. of hot ethyl acetate was mixed with a solution of 1.0542 g. of brucine in 20 cc. of hot ethyl acetate. On cooling, crystals of the brucine salt were precipitated gradually. The salt was recrystallized from ethyl acetate into several fractions with the same rotation; 23.9 mg. made up to 5 cc. with absolute ethanol at 32° gave αD −0.17; *l*, 1; $[\alpha]^{32}\text{D}$ −35°. The salt gave no evidence of mutarotation after standing for twenty-four hours at room temperature. When the salt was decomposed inactive acid was recovered.

A solution of 0.998 g. of the acid in ethyl acetate was mixed with a solution of 1.023 g. of quinine in ethyl acetate. The solution was evaporated slowly and fractions were collected at regular intervals. All fractions had the same rotation; 23.2 mg. made up to 5 cc. with absolute ethanol at 25° gave αD −0.37; *l*, 1; $[\alpha]^{25}\text{D}$ −80°. When the salt was decomposed the inactive acid was recovered.

α-Chloro-α-(2,4-dimethyl-3-chloro-6-methoxyphenyl)-ethylene.—A mixture of 30 g. of 2,4-dimethyl-3-chloro-6-methoxyacetophenone and 50 g. of phosphorus pentachloride was placed in a 200-cc. round-bottomed flask equipped with a reflux condenser attached to a gas absorption tower. A small amount of phosphorus oxychloride was added, and the mixture was heated slowly on an oil-bath until the temperature reached 120–130°. After eight hours at this temperature, the reaction mixture was allowed to cool and was poured onto cracked ice. After the phosphorus oxy-

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[4] Adams and Theobald, THIS JOURNAL, 65, 2208 (1943).

[5] Adams and Miller, *ibid.*, 62, 53 (1940); the bromopropiomesitylene was reported to be a liquid boiling at 127–129° (3 mm.). When this preparation was repeated, a solid, m. p. 43.5–44.5°, was obtained with identical chemical properties and analysis.

[6] Moureu, *Compt. rend.*, 137, 260 (1901); *Bull. soc. chim.*, 31, (3) 493, 509, 517 (1904).

chloride had hydrolyzed completely, the organic layer was separated and the aqueous layer extracted several times with ether. The combined crude product and ether extracts were washed with water and with sodium hydroxide solution and dried over anhydrous magnesium sulfate. The ether was removed and the residue was fractionated under reduced pressure. The pure product has a b. p. 105–107° (3 mm.); n^{17}_D 1.5650; d_{20} 1.2279; yield, 19.5 g. (60%).

Anal. Calcd. for $C_{11}H_{12}OCl_2$: C, 57.16; H, 5.23. Found: C, 56.64, 56.78; H, 5.18, 5.31.

The higher fractions of the original distillation were combined and chilled. The crystals which formed were separated by filtration and recrystallized from petroleum ether (b. p. 60–110°) or ethanol to give 3.7 g. (10%) of colorless crystals, m. p. 63–64° (cor.). The analysis of this material indicated it may be α-chloro-α-(2,4-dimethyl-3,5-dichloro-6-methoxyphenyl)-ethylene.

Anal. Calcd. for $C_{11}H_{11}Cl_3O$: C, 49.76; H, 4.17; Cl, 40.05. Found: C, 49.76; H, 3.98; Cl, 40.14.

2,4-Dimethyl-3-chloro-6-methoxyphenylacetylene.—In a 200-cc. 3-necked round-bottomed flask equipped with a reflux condenser, stirrer, and a dropping funnel, was prepared an ethanol solution of sodium ethoxide from 50 cc. of ethanol and 3.2 g. of sodium. The solution was heated on an oil-bath maintained at 120°, and 15.7 g. of α-chloro-α-(2,4-dimethyl-3-cdloro-6-methoxyphenyl)-ethylene in ethanol was added gradually with stirring. Heating was continued for five hours after the addition was complete, and the reaction mixture was allowed to cool. The product separated as pink platelets. The product was recrystallized from ethanol; yield, 9.5 g. (60%). The material could be purified further by sublimation under reduced pressure to give white needles, m. p. 109–110° (cor.).

Anal. Calcd. for $C_{11}H_{12}ClO$: C, 67.87; H, 5.70. Found: C, 67.84; H, 5.83.

2,4-Dimethyl-3-chloro-6-methoxyphenylpropiolic Acid.—Following the usual procedure, to the ethylmagnesium bromide prepared from 15.4 g. of ethyl bromide and 2.4 g. of magnesium was added 9.5 g. of 2,4-dimethyl-3-chloro-6-methoxyphenylacetylene. The acetylene-magnesium bromide formed was treated with carbon dioxide to give 6 g. (55%) of crude propiolic acid. On recrystallization from a mixture of benzene and petroleum ether (b. p. 60–110°) the product was obtained as white crystals; m. p. 160–161° (cor.).

Anal. Calcd. for $C_{11}H_{11}ClO_3$: C, 60.38; H, 4.65. Found: C, 60.18; H, 4.70.

β-Chloro-β-(2,4-dimethyl-3-chloro-6-methoxyphenyl)-acrylic Acid.—A solution of 1 g. of 2,4-dimethyl-3-chloro-6-methoxyphenylpropiolic acid in 30 cc. of glacial acetic acid was heated to 70–80°, and dry hydrogen chloride was bubbled into the solution for three hours. At the end of this time the reaction mixture was allowed to cool and was poured into an excess of cold water. The acid was separated by filtration and air-dried to give 1.1 g. (95%) of crude product. Recrystallization from a mixture of ethanol and water gave a white crystalline material melting at 179–180° (cor.), which did not depress the melting point of a sample of the acid previously made[3] by the reaction of phosphorus pentachloride on the appropriate substituted benzoylacetic acid.

β-Bromo-β-(2,4-dimethyl-3-chloro-6-methoxyphenyl)-acrylic Acid.—A solution of 1 g. of 2,4-dimethyl-3-chloro-6-methoxyphenylpropiolic acid in 20 cc. of warm glacial acetic acid was added to 20 ml. of constant-boiling hydrobromic acid and allowed to stand for twenty-four hours with occasional shaking. The mixture was poured into an excess of cold water; the acid was separated by filtration, washed, air-dried and recrystallized from benzene to give a yield of 1.3 g. (98%). Further recrystallization from benzene and petroleum ether (b. p. 60–110°) gave a product of m. p. 184.5–185° (cor.).

Anal. Calcd. for $C_{12}H_{12}BrClO_3$: C, 45.10; H, 3.78. Found: C, 45.53; H, 3.85.

Resolution of β-Bromo-β-(2,4-dimethyl-3-chloro-6-methoxyphenyl)-acrylic Acid.—A solution of 1.1462 g. of the bromo acid in acetone was mixed with a solution of 1.1651 g. of quinine in acetone. The acetone was removed by evaporation and the oily residue was crystallized from ethyl acetate. All of the fractions had essentially the same rotation and the rotation did not change on recrystallization; 23.8 mg. made up to 5 cc. with absolute ethanol at 27° gave α_D −0.22; *l*, 1; $[\alpha]^{27}_D$ −46.2°.

***d*-β-Bromo-β-(2,4-dimethyl-3-chloro-6-methoxyphenyl)-acrylic Acid.**—The quinine salt was decomposed by treating an aqueous suspension with ice-cold hydrochloric acid. The acid was separated by filtration and air-dried; 28.8 mg. made up to 5 cc. with absolute ethanol at 28° gave α_D +0.20; *l*, 1; $[\alpha]^{28}_D$ +34.7°.

Racemization of *d*-β-Bromo-β-(2,4-dimethyl-3-chloro-6-methoxyphenyl)-acrylic Acid.—The rate of racemization was measured both at 28° in absolute ethanol and 20° in *n*-butanol. In the former case, the following readings were taken: 0 min., 0.20; 60 min., 0.18; 145 min., 0.14; 250 min., 0.10; 345 min., 0.08; and 960 min., 0.00. From these data, the specific rate constant was calculated to be 0.00138 and the half-life, 250 min. In the latter case, racemization in *n*-butanol at 20°, the following readings were taken: 5 min., 0.178; 43 min., 0.180; 86 min., 0.170; 208 min., 0.130; 303 min., 0.108; 396 min., 0.096; 448 min., 0.085; 564 min., 0.066; and 645 min., 0.055. From these data, the specific rate constant was calculated to be 0.000954, and the half-life, 420 min.

β-Iodo-β-(2,4-dimethyl-3-chloro-6-methoxyphenyl)-acrylic Acid (XI).—A solution of 1 g. of 2,4-dimethyl-3-chloro-6-methoxyphenylpropiolic acid in 20 cc. of warm glacial acetic acid was added to 20 ml. of constant-boiling hydriodic acid. The mixture was allowed to stand for twenty-four hours with occasional shaking and was then poured into cold water. The precipitated acid was air-dried; yield 1.5 g. (98%). Recrystallization from a mixture of benzene and petroleum ether (b. p. 60–110°) gave a pure product, m. p. 180–181° (cor.).

Anal. Calcd. for $C_{12}H_{12}ClIO_3$: C, 39.31; H, 3.30. Found: C, 39.52; H, 3.43.

Attempts to resolve this acid resulted in decarboxylation and dehydrohalogenation to give 2,4-dimethyl-3-chloro-6-methoxyphenylacetylene.

4-Iodo-5,7-dimethyl-6-chlorocoumarin (XVIII).—β-Iodo-β-(2,4-dimethyl-3-chloro-6-methoxyphenyl)-acrylic acid was treated with a 1:1 mixture of constant-boiling hydriodic acid and glacial acetic acid, and was heated under reflux until solution was complete (about ten minutes). The mixture was allowed to cool and was poured into an excess of cold water. The brown flocculent precipitate was separated by filtration, washed with water and air-dried. The crude material was recrystallized from benzene and petroleum ether (b. p. 60–110°) to give light tan needles, m. p. 177–178° (cor.).

Anal. Calcd. for $C_{11}H_8ClIO_2$: C, 39.49; H, 2.14. Found: C, 39.86; H, 2.37.

When treated with hydriodic acid and glacial acetic acid under the same conditions, β-bromo-β-(2,4-dimethyl-3-chloro-6-methoxyphenyl)-acrylic acid gave the same product, indicated by a mixed melting point.

4-Bromo-5,7-dimethyl-6-chlorocoumarin.—β-Bromo-β-(2,4-dimethyl-3-chloro-6-methoxyphenyl)-acrylic acid was treated with a 1:1 mixture of constant-boiling hydrobromic acid and glacial acetic acid, and was heated under reflux for four hours. The mixture was allowed to cool and was poured into an excess of cold water. The precipitate was separated by filtration and was recrystallized from methanol to give fine white needles, m. p. 155° (cor.).

Anal. Calcd. for $C_{11}H_8BrClO_2$: C, 45.94; H, 2.80. Found: C, 46.17; H, 3.01.

Methyl 2,4-Dimethyl-3-chloro-6-methoxyphenylpropiolate.—To an ice-cold solution of one equivalent of diazomethane in ether was added 4 g. of 2,4-dimethyl-3-chloro-6-methoxyphenylpropiolic acid. The solution was filtered, and the ether was removed by evaporation. The residue was recrystallized from methanol to give 4 g. (93%) of white silky needles, m. p. 123–124° (cor.).

Anal. Calcd. for $C_{13}H_{13}ClO_3$: C, 61.79; H, 5.19. Found: C, 61.75; H, 5.22.

β-Methylthio-β-(2,4-dimethyl-3-chloro-6-methoxyphenyl)-acrylic Acid.—A mixture of 25 cc. of an ethanolic solution of sodium methyl mercaptide containing 0.035 mole of mercaptide and 3.5 g. of methyl 2,4-dimethyl-3-chloro-6-methoxyphenylpropiolate was heated under reflux for fourteen hours. Part of the ethanol was removed by distillation and the residue was poured into ice-water. The aqueous solution was extracted once with ether, and then was acidified carefully with cold dilute sulfuric acid to a congo red end-point. The crude acid was washed with water and air-dried. It was recrystallized several times from benzene to give 1.0 g. (25%) of product, m. p. 205–206° (cor.).

Anal. Calcd. for $C_{13}H_{15}ClO_3S$: C, 54.46; H, 5.27. Found: C, 54.88; H, 5.34.

Attempted Resolution of β-Methylthio-β-(2,4-dimethyl-3-chloro-6-methoxyphenyl)-acrylic Acid.—When an acetone solution of 0.490 g. of the acid was mixed with an acetone solution of 0.555 g. of quinine, and the mixture was allowed to stand for several days, a crystalline salt was formed. The salt was recrystallized into several fractions, all with the same rotation; 22.2 mg. made up to 5 cc. with absolute ethanol at 27° gave α_D −0.45; *l*, 1; $[\alpha]^{27}_D$ −101°. When the salt was decomposed with hydrochloric acid, the inactive acid was recovered.

A hot solution of 0.916 g. of brucine in acetone was mixed with a hot solution of 0.502 g. of the acid in acetone. The solution was cooled and part of the solvent was evaporated to give several crops of the brucine salt, all with the same rotation; 22.7 mg. made up to 5 cc. with absolute ethanol at 27° gave α_D −0.014; *l*, 1; $[\alpha]^{27}_D$ −31°. When the salt was decomposed, the inactive acid was recovered.

Anal. Calcd. for $C_{36}H_{41}ClN_2O_7S$: C, 63.46; H, 6.06. Found: C, 63.32; H, 6.06.

Methyl β-Methoxy-β-(2,4-dimethyl-3-chloro-6-methoxyphenyl)-acrylate.—To the ether solution of diazomethane prepared from 20 g. of nitrosomethylurea, was added slowly 10 g. of 2,4-dimethyl-3-chloro-6-methoxybenzoylacetic acid prepared according to the directions of Adams and Gross.[3] After forty-eight hours, the solution was filtered and evaporated to dryness. The residue was recrystallized from methanol to give 6.5 g. (58%), then from petroleum ether (b. p. 60–110°) to give white crystalline material, m. p. 101–101.5° (cor.).

Anal. Calcd. for $C_{14}H_{17}ClO_4$: C, 59.05; H, 6.02. Found: C, 59.38; H, 6.11.

β-Methoxy-β-(2,4-dimethyl-3-chloro-6-methoxyphenyl)-acrylic Acid.—A mixture of 5 g. of methyl β-methoxy-β-(2,4-dimethyl-3-chloro-6-methoxyphenyl)-acrylate with 15% methanolic potassium hydroxide prepared by mixing 25 cc. of methanol, 5 cc. of water and 5 g. of potassium hydroxide, was heated under reflux. After twelve hours, the solution was allowed to cool and part of the methanol was removed by evaporation. The residue was diluted with water, and the alkaline solution was carefully neutralized with dilute sulfuric acid. The precipitated acid was washed with water. While still wet, the acid was dissolved in benzene, the benzene solution was decanted from the water layer, and the solution was evaporated to dryness to give 4 g. (88%) of product, m. p. 163–165° (cor.). Recrystallization always gave a product with a lower melting point.

Anal. Calcd. for $C_{13}H_{15}ClO_4$: C, 57.67; H, 5.59. Found: C, 57.91; H, 5.91.

Attempted Resolution of β-Methoxy-β-(2,4-dimethyl-3-chloro-6-methoxyphenyl)-acrylic Acid.—A salt was prepared from 0.986 g. of the acid and 1.196 g. of quinine, but all fractions showed the same rotation; 23.2 mg. made up to 5 cc. with absolute ethanol at 27° gave α_D −0.39; *l*, 1; $[\alpha]^{27}_D$ −84°. When the salt was decomposed the inactive acid was recovered.

Summary

1. α-Methyl-β-methoxy-β-(2,4,6-trimethyl-3-bromophenyl)-acrylic acid has been prepared from α-methyl-2,4,6-trimethyl-4-bromobenzoylacetic acid. It could not be resolved, thus demonstrating the ineffectiveness of a methoxyl in the β-position.

2. 2,4-Dimethyl-3-chloro-6-methoxyacetophenone was converted to α-chloro-α-(2,4-dimethyl-3-chloro-6-methoxyphenyl)-ethylene which was dehydrohalogenated to 2,4-dimethyl-3-chloro-6-methoxyphenylacetylene. This acetylene through the magnesium salt was carbonated to 2,4-dimethyl-3-chloro-6-methoxyphenylpropiolic acid.

3. The propiolic acid mentioned in (2) was submitted to the action of hydrogen chloride, hydrogen bromide, and hydrogen iodide, each in glacial acetic acid, and in the form of its ester to the action of sodium methyl mercaptide and of sodium methylate. Thus, there was obtained the β-chloro, β-bromo, β-iodo and β-methylthio derivatives of β-(2,4-dimethyl-3-chloro-6-methoxyphenyl)-acrylic acid. The β-methoxy derivative did not form and this analog was synthesized through the appropriate aroylacetic acid. The β-chloro compound was identical with that obtained through the aroylacetic acid route.

4. The β-bromo compound was resolved and its half-life period was four hundred and twenty minutes in contrast to nine minutes for the corresponding β-chloro analog. The β-iodo derivative decomposed in the presence of alkaloids; the β-methylthio and β-methoxy could not be resolved.

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