Table II. Phase Diagram Maxima

| Compound | M.P.[a] |
|---|---|
| *o*-nitroaniline chloropicrate | 100° |
| naphthalene chloropicrate | 128° |
| anthracene chloropicrate | 152° |
| naphthalene bromopicrate | 113° |
| anthracene bromopicrate | 184° |
| anthracene iodopicrate | 164° |
| *m*-nitroaniline *tert*-butylpicrate | 156° |
| *p*-nitroaniline *tert*-butylpicrate | 147° |
| naphthalene *tert*-butylpicrate | 133° |
| anthracene *tert*-butylpicrate | 183° |
| hexamethylbenzene *tert*-butylpicrate | 149° |
| naphthalene methoxypicrate | 78° |
| anthracene methoxypicrate | 188° |
| hexamethylbenzene methoxypicrate | 139° (1:2) |
| hexamethylbenzene methoxypicrate | 120° (2:1) |

[a] M.P. are taken from maxima of phase diagrams indicating 1:1 compound formation except as indicated.

The infrared spectra of all isolable compounds in this research were determined and found to be very similar to those previously reported (*4*).

## EXPERIMENTAL

Microanalyses were by Microtech Laboratories, Skokie, Ill. All infrared spectra were recorded on a Perkin-Elmer, Model 21, spectrophotometer using nujol mulls.

Preparation of picric acids: chloro-, bromo-, and iodopicric acids were prepared by the method of Hodgson and coworkers (*2*, *3*). The preparation of *m*-*tert*-butylphenol followed the method of Carpenter (*1*). Nitration of this phenol was done by the method of Moore (*5*).

The nitration of *m*-fluorophenol followed the method of Hodgson and Nixon (*3*). Recrystallization of the solid, using water as a solvent, gave light yellow crystals, m.p. 168–172°. The infrared spectrum of this material closely matched that of an authentic sample of styphnic acid and a mixed melting point of this material with styphnic acid showed no depression.

Methoxypicric acid was prepared by nitrating *m*-methoxyphenol by the method of Moore (*5*).

The methods used in the preparation of the 3-substituted picrates of hydrocarbons and amines, the melting points of these compounds, and the phase diagrams have been previously described (*4*).

Hexamethylbenzene chloropicrate and bromopicrate were obtained analytically pure from the reaction mixture and did not require recrystallization. Hexamethylbenzene chloropicrate: orange crystals (m.p. 146–148°d). *Anal:* Calc. for $C_{18}H_{20}N_3O_7Cl$: 9.86%N; Found 9.75%N. Hexamethylbenzene bromopicrate: orange crystals (m.p. 148–150° d). *Anal:* Calcd. for $C_{18}N_{20}N_3O_7Br$: 8.93%N; Found 9.08%N.

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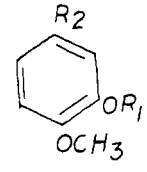
# Synthesis of 3-Hydroxy-4-methoxybutyrophenone


HERBERT S. VERTER, C. O. VAN CAMP, L. DeVRIES, R. HAFFNER, and R. HOAG
Central Michigan University, Mount Pleasant, Mich.



**Friedel-Crafts condensation of guaiacol with butyric anhydrides using a phosphoric acid catalyst produces 3-butyroxy-4-methoxybutyrophenone whereas condensation using aluminum chloride or polyphosphoric acid catalysts produces 3-methoxy-4-hydroxybutyrophenone. A possible explanation of the unique nature of phosphoric acid is offered.**


ALTHOUGH A NUMBER of ketonic derivatives of guaiacol have been prepared by Friedel-Crafts acylation, the side chain introduced by the acylation normally is directed para to the phenolic group (*4*, *5*) rather than para to the methoxyl group (*6*). The acylation probably proceeds by way of a Fries rearrangement of the phenolic ester formed initially (*1*). We were interested in introducing an acyl group para to the methoxyl group in guaiacol, and have synthesized one such compound, 3-hydroxy-4-methoxybutyrophenone (I). Acylation of guaiacol with butyric anhydride and syrupy phosphoric acid yielded a mixture of guaiacol butyrate (II) and 3-butyroxy-4-methoxybutyrophenone (III). The latter compound was hydrolyzed to I with sodium methoxide in methanol.




I. $R_1 = H$, $R_2 = COCH_2CH_2CH_3$
II. $R_1 = COCH_2CH_2CH_3$, $R_2 = H$
III. $R_1 = COCH_2CH_2CH_3$, $R_2 = COCH_2CH_2CH_3$
IV. $R_1 = H$, $R_2 = COC(=NOH)CH_2CH_3$
V. $R_1 = COCH_3$, $R_2 = COC(=NOCOCH_3)CH_2CH_3$

Friedel-Crafts acylation of guaiacol with aluminum chloride or with polyphosphoric acid directed the butyryl

side chain para to the phenolic group. Early studies with these catalysts were abandoned. The unique nature of syrupy phosphoric acid in this reaction seems to be due to the inability of this acid to catalyze a Fries rearrangement of guaiacol butyrate under the conditions employed. The methoxyl group on the initially formed guaiacol butyrate orients the incoming acylium ion more effectively than the ester group to produce the observed ketone.

The position of the ketonic side chain was established by nitrosation of ketone III to 1-(3′-hydroxy-4′-methoxyphenyl)-1,2-butanedione-2-oxime (IV) followed by abnormal Beckmann rearrangement (*2*) of this oxime to produce isovanillic acid. If oxime IV is treated with acetic anhydride in pyridine, a mixture of 1-(3′-acetoxy-4′-methoxyphenyl)-1,2-butanedione-2-oxime-0-acetate (V) and 3-acetoxy-4-methoxybenzoic acid is produced. Isolation of 3-acetoxy-4-methoxybenzoic acid under the mild conditions used in this acetylation gives some indication of the ease with which oxime IV undergoes abnormal Beckmann rearrangement. Both isovanillic acid and 3-acetoxy-4-methoxybenzoic acid were identified with authentic samples (*3*) by mixture melting point determination and comparison of the infrared spectra.

## EXPERIMENTAL

Melting points were determined on a Kofler micro hot stage and are corrected. The infrared spectra were obtained in Nujol mulls on a Perkin-Elmer Infracord, Model 137.

**3-Butyroxy-4-methoxybutyrophenone (III).** Guaiacol (245 grams, 2 moles), butyric anhydride (790 grams, 5 moles) and syrupy phosphoric acid (15 grams, 0.15 mole) were refluxed together for five hours. The reaction mixture was poured into 10 liters of water, allowed to stand for one hour, and then extracted with one liter of ether. The ether extract was washed with 5% sodium carbonate solution and dried with sodium sulfate. The ether was evaporated. The black, oily residue was distilled at reduced pressure. After a large forerun, which consisted mainly of guaiacol butyrate (II), b.p. 115–145° (1 mm. of Hg), the crude 3-butyroxy-4-methoxybutyrophenone distilled, b.p. 185–190° (1 mm. of Hg). The product thus obtained (103 grams, 21%) crystallized from ether-pentane as large, transparent plates, m.p. 42–43°. *Anal.* Calcd. for $C_{15}H_{20}O_4$: C, 68.2; H, 7.63. Found: C, 68.3; H, 7.71.

**3-Hydroxy-4-methoxybutyrophenone (I).** To a solution of two grams (8 mmoles) of 3-butyroxy-4-methoxybutyrophenone in 8 ml. of absolute methanol was added 4 ml. of 2*N* sodium methoxide in methanol (8 mmoles). The solution stood overnight at room temperature, then was poured into 20 ml. of water, acidified with concentrated hydrochloric acid, and extracted with 40 ml. of ether. The ether extract was washed with 5% sodium bicarbonate solution and extracted with 10% sodium hydroxide solution. The basic extract was acidified with concentrated hydrochloric acid and extracted with methylene chloride. The dried methylene chloride extract was evaporated to dryness. The crude 3-hydroxy-4-methoxybutyrophenone thus obtained (1.3 grams, 82%) recrystallized from cyclohexane as glistening platelets, m.p. 81–82°. *Anal.* Calcd. for $C_{11}H_{14}O_3$: C, 68.0; H, 7.27. Found: C, 67.9; H, 7.09.

**1-(3′-Hydroxy-4′-methoxyphenyl)-1,2-butanedione -2-oxime (IV).** To a cooled solution of 368 mg. (1.4 mmoles) of 3-butyroxy-4-methoxybutyrophenone in two ml. of methylene chloride was added 0.3 ml. of ether saturated with hydrogen chloride and 165 mg. (1.6 mmoles) of *n*-butyl nitrite. The mixture was let stand overnight at 50°, then poured into 5 ml. of methylene chloride and extracted with several portions of cold 10% sodium hydroxide solution. The base extract was immediately acidified with concentrated hydrochloric acid and extracted with dichloromethane. The dried dichloromethane extract was evaporated to dryness. The residue was dissolved in one ml. of benzene and set aside to crystallize. After standing one day at 4°, the crystals were separated by filtration. The crude 1-(3′-hydroxy-4′-methoxyphenyl)-1,2-butanedione-2-oxime thus obtained (71 mg., 32%), crystallized from alcohol-benzene as white needles, m.p. 134–135°. *Anal.* Calcd. for $C_{11}H_{13}NO_4$: C, 59.2; H, 5.87. Found: C, 59.4; H, 5.89.

**1-(3′-Acetoxy-4′-methoxyphenyl)-1,2-butanedione -2-oxime-O-acetate (V).** To a solution of 100 mg. of 1-(3′-acetoxy-4′-methoxyphenyl)-1,2-butanedione-2-oxime (IV) in 3 ml. of pyridine was added with cooling 2 ml. of acetic anhydride. The solution was let stand at room temperature for one day, then poured into water and extracted with ether. The ether extract was washed with 1*N* hydrochloric acid, extracted with dilute sodium bicarbonate solution and the dried ether layer evaporated to dryness. The crude 1-(3′-acetoxy -4′- methoxyphenyl) -1,2- butanedione-2-oxime-*O*-acetate thus obtained (121 mg.) crystallized from ether-pentane as white needles, m.p. 89–90°. *Anal.* Calcd. for $C_{15}H_{17}NO_6$: C, 58.6; H, 5.58; N, 4.56. Found: C, 58.3; H, 5.60; N, 4.44.

Acidification of the bicarbonate extract yielded four mg. of 3-acetoxy-4-methoxybenzoic acid, m.p. 210° [lit. (*3*) m.p. 206–207°].

**Isovanillic acid.** To a solution of 100 mg. of oxime IV in four ml. of dioxane was added four ml. of 20% sulfuric acid and the solution heated on the steam bath for thirty minutes. The reaction mixture was allowed to stand overnight at room temperature, during which time 21 mg. of isovanillic acid crystallized, m.p. 250° [lit. (*3*) m.p. 250°].

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