Experimental[10]

The acylation of ketones with various anhydrides was carried out according to the general procedure described previously[3] for the acetylation of ketones with acetic anhydride, using 0.5 mole of the ketone and 1.0 mole of the anhydride, except with methyl ethyl ketone and *n*-caproic anhydride which were used in one-half these quantities. The methyl and methylene derivatives obtained from methyl-methylene ketones were separated by the alkali extraction method described previously.[3] The yields and other data for the β-diketones are given in Table I.

With acetic anhydride (1.0 mole) and di-isopropyl ketone (0.5 mole) there was obtained 20 g. of product, b. p. 107–108 at 25 mm., which did not give the correct analysis for the corresponding β-diketone, dimethyl isobutyrylacetone. *Anal.* Calcd. for $C_9H_{16}O_2$: C, 69.19; H, 10.32. Found: C, 62.29, 62.04; H, 9.85, 9.88.

(10) Boiling points and melting points are uncorrected. Analyses are by Dr. T. S. Ma, Microchemical Laboratory, University of Chicago, Chicago, Illinois.

Summary

1. The acylation of ketones with anhydrides by means of boron trifluoride to form β-diketones has been shown to be quite general with purely aliphatic anhydrides and various ketones having α-hydrogen.

2. The reaction is of particular value for the synthesis of a number of β-diketones, for certain of which the more common basic reagent method is not suitable.

DURHAM, N. C. RECEIVED SEPTEMBER 9, 1944

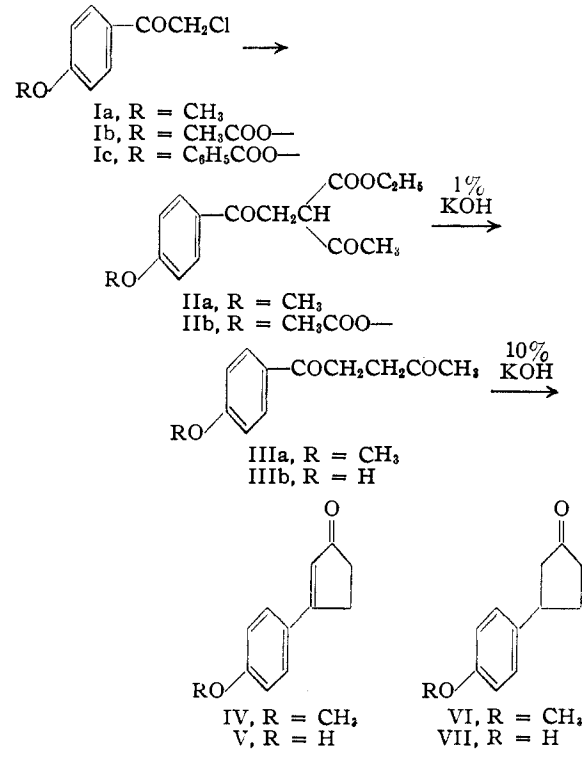
[CONTRIBUTION FROM THE LABORATORY OF ORGANIC CHEMISTRY OF THE UNIVERSITY OF WISCONSIN]

The Synthesis of 3-(*p*-Hydroxyphenyl)-cyclopentanone-1 and Related Compounds

BY A. L. WILDS AND THOMAS L. JOHNSON

As intermediate compounds in a projected synthesis, we were interested in preparing 3-(*p*-hydroxyphenyl)-cyclopenten-2-one-1 (V) and its reduction product 3-(*p*-hydroxyphenyl)-cyclopentanone-1 (VII). For this purpose we have employed the method which Borsche and co-workers[1] used a number of years ago for the synthesis of the corresponding compounds lacking the hydroxyl group.

p-Methoxyphenacyl chloride (Ia) was condensed with the sodio derivative of ethyl acetoacetate, giving the intermediate IIa, which upon treatment with aqueous potassium hydroxide underwent cyclization with loss of the carbethoxyl group to form the substituted cyclopentenone IV. This method of Borsche has been used in recent years by Robinson[2] and Weidlich[3] and their coworkers to prepare naphthylcyclopentenones and by Wilds[4] for the synthesis of an analogous ketocyclopentenophenanthrene derivative. In the present case considerable attention was devoted to finding the most favorable conditions for effecting the transformation of IIa into IV. Ultimately this was accomplished by warming the keto ester IIa with 1% potassium hydroxide for one and one-half hours, a process which resulted in the formation of the diketone IIIa, followed by refluxing with 10% alkali to effect the cyclization. In this manner, without isolation of intermediates, the cyclopentenone derivative IV was obtained in 65% over-all yield from *p*-methoxyphenacyl chloride. When the reaction was stopped after the action of 1% alkali, the crystalline diketone IIIa could be isolated. The latter was converted to IV in 93% yield when heated for two hours with stronger alkali.



Selective hydrogenation of the carbon–carbon double bond of IV, using a palladium–charcoal catalyst, gave the crystalline cyclopentanone derivative VI in 63% yield. It was possible to demethylate the reduction product VI by the action of hydrobromic and acetic acids, although the yield of the phenol VII was rather low (39%), due to condensation. The unsaturated ketone IV was even more sensitive toward this demethyl-

(1) (a) Borsche and Menz, *Ber.*, **41**, 190 (1908); (b) Borsche and Fels, *ibid.*, **39**, 1809 (1906).

(2) Koebner and Robinson, *J. Chem. Soc.*, 566 (1941).

(3) Weidlich and Daniels, *Ber.*, **72**, 1590 (1939); Weidlich and Meyer-Delius, *ibid.*, **72**, 1941 (1939).

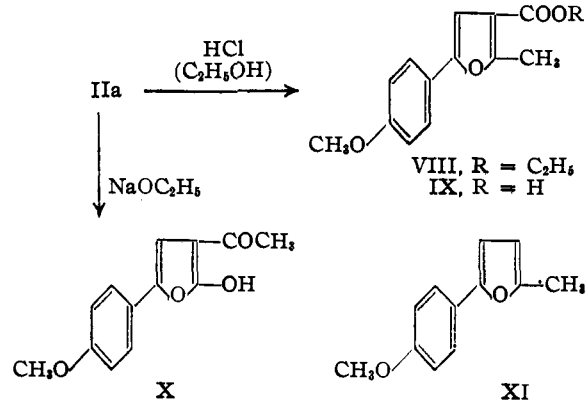
(4) Wilds, THIS JOURNAL, **64**, 1421 (1942).

ation reagent, and the phenol V was obtained in only 5% yield. When aluminum chloride was used in boiling carbon disulfide, however, a much cleaner demethylation reaction occurred with IV, resulting in a 54% yield of the pure phenolic ketone V. Under similar conditions VI was recovered practically unchanged. Selective reduction of the phenol V did not take place as smoothly as in the case of the methyl ether. Instead, when one mole of hydrogen had been absorbed, a mixture of reduction products resulted which contained 22% of the phenol VII accompanied by unhydrogenated material.

As an alternative route to the phenolic ketones, the corresponding reactions of esters of *p*-hydroxyphenacyl chloride were investigated. The acetate Ib was used to prepare the keto ester IIb, which upon mild hydrolysis gave the diketone IIIb, although in only 21% yield. Cyclization of this compound took place much less readily than in the case of the methyl ether, and the resulting yield of the ketone V was lower (65% yield in thirteen hours). This relative unreactivity of the carbonyl group can be ascribed to the presence of the phenolic hydroxyl group (as the phenoxide ion) in the para position. When the benzoate Ic was employed and converted into the ketone V without isolation of the intermediates, the overall yield was 28%. In view of the lower yields in these series, the phenolic derivatives V and VII are more readily prepared through their methyl ethers, followed by demethylation. It will be of interest to test these phenolic ketones to see if they possess estrogenic activity.[5]

In addition to the alkaline cyclization of the substituted acetoacetic ester IIa to the cyclopentenone IV, some of the cyclization reactions effected by other reagents were investigated. Hydrogen chloride in alcohol resulted in the formation of the furan carboxylic ester VIII in 65% yield. By hydrolysis to the acid IX, followed by decarboxylation, this was converted into the furan derivative XI. Borsche and Fels have prepared similar compounds from phenacylacetoacetic ester.[1b] The critical effect which the exact conditions have upon the course of the reaction is strikingly illustrated by the fact that concentrated hydrochloric acid (or alcoholic hydrogen chloride) converted IIa into the furan ester VIII, equal amounts of hydrochloric and acetic acids led to the diketone IIIa, while one part of hydrochloric acid to three parts of acetic acid resulted in a mixture of the diketone and furan ester.

(5) Another possible route to the reduced ketones VI and VII involves the Reformatsky reaction between methyl β-*p*-anisoylpropionate and methyl bromoacetate, followed by reduction of the resulting lactone ester and cyclization (*cf.* the method used by Banerjee, *Science and Culture*, **5**, 566 (1940) for the synthesis of 3-(*p*-hydroxyphenyl)-cyclohexanone, and quite recently by Bachmann and Morin, THIS JOURNAL, **66**, 553 (1944) for naphthylcyclopentanones). Preliminary experiments by James M. Higbee (in 1941) indicated that this synthesis was feasible, although in lower over-all yields than those given above.



As was the case with the cyclic acetoacetic ester derivative recently prepared from 2-bromo-1-ketotetrahydrophenanthrene,[4] sodium ethoxide converted IIa into the enol lactone, with the elimination of alcohol. This product may be formulated as the hydroxy-furan X, or as the isomeric lactone in which enolization involves the acetyl group rather than the carbonyl group of the lactone ring. Borsche[1b] preferred the latter structure for the corresponding compound from phenacylacetoacetic ester. Unlike the hydroxy-furan from the ketotetrahydrophenanthrene derivative, which gave 2-phenanthrene-acetone upon heating, X was stable toward heat and could be distilled unchanged under reduced pressure.

Experimental[6]

***p*-Methoxyphenacyl Chloride (Ia).**—The following procedure is similar to that of Fusco,[7] except the amount of aluminum chloride was reduced to one equivalent. Thirty-eight grams (0.28 mole) of anhydrous aluminum chloride was added over a period of one-half hour to a mixture of 30 g. (0.28 mole) of anisole, 36 g. (0.32 mole) of chloroacetyl chloride and 60 cc. of carbon disulfide, stirred mechanically and cooled in a bath at 10°. One-half hour after addition was complete the cooling bath was removed and the mixture heated to reflux for fifteen minutes. Stirring was continued at room temperature for another fourteen hours, the solvent decanted and the residue hydrolyzed with ice and hydrochloric acid. The crude product obtained by filtration (42 g. or 82%, m. p. 50–95°) was recrystallized once from ethanol to give 23 g. (45% yield) of the para isomer as nearly colorless needles, m. p. 96–99°. The mother liquor contained a mixture of the ortho and para isomers.

***p*-Acetoxyphenacyl Chloride (Ib).**—To a solution of 94 g. of phenol in 250 cc. of *sym*-tetrachloroethane was added slowly with stirring 267 g. of anhydrous aluminum chloride. The mixture was then heated to 70° in an oil-bath and a solution of 75 g. of chloroacetyl chloride in 100 cc. of tetrachloroethane was added over a period of one hour and the solution stirred for five hours at 70° and an additional ten hours without further heating. After hydrolysis with ice and hydrochloric acid, the insoluble product was filtered and washed thoroughly with dilute acid and water, giving 100 g. of brown solid with the m. p. 90–137°. This mixture of phenolic ketones was converted to the acetate by dissolving in 300 cc. of dioxane, adding 140 cc.

(6) All m. ps. are corrected unless otherwise indicated.

(7) Fusco, *Ann. chim. applicata*, **30**, 324 (1940): the 88% yield mentioned in the abstract of this article [*C. A.*, **35**, 3621 (1941)] refers to a crude mixture of isomers rather than to the pure para isomer. See also Tutin, *J. Chem. Soc.*, **97**, 2503 (1910), and Kunckell and Jobannsen, *Ber.*, **30**, 1715 (1897).

of acetyl chloride and allowing to stand at room temperature for fifteen hours, followed by one-half hour at reflux. The solution was concentrated, filtered and the product recrystallized twice from ethanol (Norit) to give 40 g. (28% yield, based upon the chloroacetyl chloride used) of the *p*-acetoxy ketone with the m. p. 88–90°. After another recrystallization of the solid the m. p. was 89–90° (reported 89–90°).[8]

Benzoate of *p*-Hydroxyphenacyl Chloride (Ic).—The crude phenolic ketone (37.5 g.), prepared from 28 g. of chloroacetyl chloride as described above, was recrystallized from dioxane and then from benzene–ethanol giving 17 g. of the para isomer, m. p. 147–151°.[9] The benzoylation of this material required rather drastic conditions, since it was not possible to use pyridine as a catalyst due to the reactive chlorine atom. A solution of the phenol (17 g.) and 42 g. of benzoyl chloride in 100 cc. of dioxane was warmed on the steam-bath overnight, 30 g. of additional benzoyl chloride added and the solution refluxed twelve hours longer. After addition of bicarbonate solution the solid was filtered, dried and recrystallized from ethanol, to give 20 g. of the benzoate or a 29% over-all yield, based upon the chloroacetyl chloride; m. p. 117.5–118.5°. Another recrystallization gave colorless blades with the m. p. 118.5–119.5°. Priestley and Moness[10] prepared this compound with the m. p. 115° by the action of benzoic acid and phosphorus oxychloride on the corresponding phenol, but reported no analysis.

Anal. Calcd. for $C_{15}H_{11}O_3Cl$: C, 65.6; H, 4.0. Found: C, 65.2; H, 3.9.

Ethyl *p*-Methoxyphenacylacetoacetate (IIa).—To the sodio derivative prepared from 4 g. of sodium powder and 30 cc. of ethyl acetoacetate in 200 cc. of dry, thiophene-free benzene was added 20 g. of *p*-methoxyphenacyl chloride and the mixture was refluxed for six hours. After cooling, the benzene solution was washed twice with 5% alkali and with water. Evaporation of the solvent left 24 g. (80%) of the crude substituted acetoacetic ester as a brown oil. This material was used for some of the reactions described below, except where otherwise noted. For most of the reactions the ester was not extracted with alkali since this removed some of the product as the salt of the keto acid. When a small amount of absolute alcohol was used in conjunction with the benzene in the preparation of the sodio derivative the yields were lowered to 60–75%.

***p*-Methoxyphenacylacetone (IIIa), (a) Alkaline Hydrolysis.**—A mixture of 2 g. of the crude *p*-methoxyphenacylacetoacetic ester and 200 cc. of 1% potassium hydroxide was refluxed with stirring for two hours under a nitrogen atmosphere. The cooled solution was extracted with benzene and the latter washed with dilute alkali and water. Evaporation of the solvent followed by recrystallization of the residue from 60–68° petroleum ether gave a total of 0.91 g. (61%) of the diketone melting at 53–56° with a slight residue, indicating the presence of a trace of the cyclic ketone described below. Further recrystallization from 90–100° petroleum ether gave the pure compound as colorless blades with the m. p. 56.5–57°. Helberger[11] reported obtaining the compound as an oil in low yield by the action of levulinyl chloride and aluminum chloride on anisole.

Anal. Calcd. for $C_{12}H_{14}O_3$: C, 69.9; H, 6.8. Found: C, 70.0; H, 7.1.

(b) Acid Hydrolysis.—The diketone also was obtained by hydrolysis of 6 g. of the crude substituted acetoacetic ester by refluxing with 30 cc. of acetic acid and 30 cc. of concentrated hydrochloric acid for five hours under carbon dioxide. The resulting dark mixture was extracted with benzene, washed with dilute alkali and water and the residue evaporatively distilled at 130–150° (0.2 mm.). Recrystallization of the distillate (2.8 g.) from 60–68° petroleum ether gave a total of 2.25 g. (51% yield) of pure diketone with the m. p. 56–57°. When the ester IIa was refluxed with 30 cc. of hydrochloric acid and 90 cc. of acetic acid for seven hours, a mixture of the diketone and the furan ester VIII was obtained.

3-(*p*-Methoxyphenyl)-cyclopenten-2-one-1 (IV).—Fifteen grams of *p*-methoxyphenacyl chloride was converted into the substituted acetoacetic ester as described above, except the benzene solution was not washed with alkali. Instead it was evaporated in a 3-liter, 3-necked flask which was equipped with a Hershberg stirrer, dropping funnel and reflux condenser attached to a mercury trap. The flask was filled with nitrogen and 1250 cc. of 1% potassium hydroxide solution, heated to the boiling point to remove dissolved air, was added and the mixture refluxed and stirred for one and one-half hours. Then a solution of 145 g. of potassium hydroxide in 150 cc. of water was added and the resulting 10% alkaline solution refluxed for two hours longer. By cooling, filtering and extracting the filtrate with benzene, a total of 11.6 g. of light-brown ketone was obtained with the m. p. 127–138°. Recrystallization from ethanol gave a total of 10.0 g. (65%) of material melting at 138.5–140.5°. The pure ketone crystallized from ethanol as colorless needles, m. p. 140–141°. It gave only a pale-yellow color with concentrated sulfuric acid.

Anal. Calcd. for $C_{12}H_{12}O_2$: C, 76.6; H, 6.4. Found: C, 76.7; H, 6.7.

When 5 to 10% alkali was used directly on the acetoacetic ester derivative, the yield was lower (40–45%) with considerable material in the acidic fraction. In the above procedure this crude acid, which contained *β*-*p*-methoxybenzoylpropionic acid, amounted to 2.6 g. (15%).

The cyclic ketone also was obtained in 93% yield (m. p. 138–140°) by refluxing 1 g. of *p*-methoxyphenacylacetone with 100 cc. of 10% potassium hydroxide for two hours under nitrogen.

The **oxime** of the ketone was prepared in 85% yield in alcohol–pyridine solution. The compound crystallized from ethanol as colorless leaflets, m. p. 189–191.5° (with decomposition and previous darkening at 188°). It gave a vermillion color with sulfuric acid.

Anal. Calcd. for $C_{12}H_{13}O_2N$: C, 70.9; H, 6.4. Found: C, 71.3; H, 6.5.

The **2,4-dinitrophenylhydrazone** was prepared in 92% yield in alcohol with a small amount of hydrochloric acid. It crystallized from toluene as brilliant red blades which sintered at 250° and melted with decomposition at 252–253° (uncor.).

Anal. Calcd. for $C_{18}H_{16}O_5N_4$: C, 58.7; H, 4.4. Found: C, 58.9; H, 4.3.

3-(*p*-Methoxyphenyl)-cyclopentanone-1 (VI).—A solution of 1.86 g. of the unsaturated ketone, purified by evaporative distillation at 160–180° (0.1 mm.) and recrystallization from ethanol, in 50 cc. of pure dioxane was shaken in an atmosphere of hydrogen with 0.75 g. of palladium–charcoal catalyst[12] at room temperature and pressure. The reaction was stopped after five and one-half hours when approximately 10% more than one mole-equivalent of hydrogen had been absorbed; further hydrogenation appeared to be taking place. The catalyst and solvent were removed leaving a pale yellow oil which was dissolved in 5 cc. of methanol, cooled in Dry Ice–alcohol and scratched. In this manner a total of 1.18 g. (63%) of colorless crystals was obtained with the m. p. 42–45.5°. An additional 0.6 g. of the oil could not be crystallized. Recrystallization of the ketone from 60–68° petroleum ether gave colorless prisms, m. p. 47–49°. The crystals dissolved in sulfuric acid to give a yellow solution.

Anal. Calcd. for $C_{12}H_{14}O_2$: C, 75.8; H, 7.4. Found: C, 75.8; H, 7.4.

The **2,4-dinitrophenylhydrazone,** prepared in 91% yield, crystallized from benzene as bright-red rhombic plates; m. p. 183.5–185.5°.

Anal. Calcd. for $C_{18}H_{18}O_5N_4$: C, 58.4; H, 4.9. Found: C, 58.5; H, 4.7.

(8) Tutin, Caton and Hann, *J. Chem. Soc.*, **95**, 2119 (1909).

(9) Allewelt and Day, *J. Org. Chem.*, **6**, 386 (1941).

(10) Priestley and Moness, *ibid.*, **5**, 357 (1940).

(11) Helberger, *Ann.*, **522**, 278 (1936).

(12) Zelinsky and Turowa-Pollak, *Ber.*, **58**, 1295 (1925).

***p*-Hydroxyphenacylacetone (IIIb).**—To the sodioacetoacetic ester prepared from 1.11 g. of sodium powder and 8.2 cc. of ethyl acetoacetate in 100 cc. of dry, thiophene-free benzene was added a solution of 8 g. of *p*-acetoxyphenacyl chloride in a small amount of warm benzene and the mixture was refluxed for three hours. The benzene was washed with dilute acetic acid and water and filtered to remove about 1 g. of insoluble material. Upon evaporation 10.1 g. of an oil was obtained which did not crystallize. This was stirred with 750 cc. of 1% potassium hydroxide solution at room temperature for six hours, filtered to remove a small amount of gummy solid, acidified to congo red with hydrochloric acid and refluxed for one-half hour. After cooling an excess of sodium bicarbonate was added, the mixture was extracted twice with ether and the latter washed with bicarbonate solution, water and dried over sodium sulfate. Evaporation of the ether gave a light-brown oil which rapidly crystallized. This was triturated with 40–60° petroleum ether and filtered to give 1.83 g. of yellow diketone (25% over-all yield from *p*-acetoxyphenacyl chloride); m. p. 80–90°. Recrystallization from benzene gave 1.50 g. (21%) of material melting at 92–95° with a small amount of higher melting residue. The latter could be removed by dissolving the solid in a small amount of ether, filtering and recrystallizing from benzene. The pure diketone was obtained as colorless blades with the m. p. 99–100°. It gave no color with alcoholic ferric chloride.

Anal. Calcd. for $C_{11}H_{12}O_3$: C, 68.7; H, 6.3. Found: C, 68.7; H, 6.1.

The diketone also could be obtained in 10–15% yield by refluxing the substituted acetoacetic ester with a mixture of hydrochloric and acetic acids under nitrogen for six hours. Two evaporative distillations of the phenolic fraction at 160–180° (0.2 mm.) and recrystallization from benzene gave material melting at 98–99°, and showing no depression in m. p. when mixed with the diketone prepared by means of dilute alkali.

3-(*p*-Hydroxyphenyl)-cyclopenten-2-one-1 (V). (a) From *p*-Hydroxyphenacylacetone.—A solution of 1.36 g. of the hydroxy diketone IIIb in 500 cc. of 5% potassium hydroxide solution was refluxed for thirteen hours under nitrogen. After cooling and acidifying, 0.80 g. (65%) of buff-colored solid was obtained; m. p. 225–232° (dec.). Vacuum sublimation at 210–220° (0.4 mm.) gave 0.70 g. (57%) of material with the m. p. 231–234.5° (dec.). When only five hours of heating was used, cyclization was incomplete and approximately 30% of the starting material was recovered. The pure phenolic ketone was obtained from ethanol as colorless leaflets with the m. p. 234.0–236.0° (Pyrex m. p. tube evacuated to 0.5 mm.). The compound gave a yellow color with sulfuric acid but no color with alcoholic ferric chloride solution.

Anal. Calcd. for $C_{11}H_{10}O_2$: C, 75.8; H, 5.8. Found: C, 75.5; H, 5.6.

(b) From the Benzoate of *p*-Hydroxyphenacyl Chloride.—Ten grams of this ester was added to the sodioacetoacetic ester prepared from 1.7 g. of sodium powder and 14 cc. of ethyl acetoacetate in 100 cc. of dry benzene. After refluxing for four hours, the benzene layer was washed with dilute acetic acid, water and evaporated. The residual oil was refluxed and stirred under nitrogen with 750 cc. of 1% potassium hydroxide solution for two and one-half hours. The concentration of alkali was then raised to 5% by the addition of concentrated potassium hydroxide solution and the mixture was refluxed fifteen hours longer. After cooling, acidifying and adding an excess of sodium bicarbonate, a light brown solid separated which was redissolved in ethanol and filtered to remove inorganic material. Sublimation of the product at 200–220° (0.4 mm.) gave 1.8 g. of the phenolic ketone for an over-all yield of 28% from the phenacyl chloride derivative; m. p. 230–234° (dec.).

(c) By Demethylation of the Methyl Ether.—A mixture of 0.5 g. of the methyl ether, obtained by cyclization as described earlier, 25 cc. of carbon disulfide and 2.5 g. of anhydrous aluminum chloride was refluxed and stirred for nineteen hours. The reaction mixture was then hydrolyzed with dilute hydrochloric acid and filtered. This material was dissolved in warm 5% potassium hydroxide, filtered and the solution acidified and extracted with ether, from which 0.34 g. (73%) of the phenol was obtained; m. p. 225–229° (dec.). Sublimation and recrystallization from methanol gave 0.25 g. (54%) of pure material with the m. p. 234.0–236.0° (evacuated Pyrex tube). No depression in m. p. was observed when this product was mixed with the material obtained in (a) above. When the demethylation was carried out at room temperature, the yield of crude phenolic material was only 45%. In benzene at room temperature the extent of reaction was slight. An attempt to effect demethylation by refluxing with a mixture of hydrobromic and acetic acids for five hours led mainly to a high-melting, reddish resin and only 5% of the desired phenolic compound.

The **benzoate** of the phenol was prepared with benzoyl chloride in dioxane-pyridine in 80% yield. The compound crystallized from ethanol as colorless leaflets or blades, m. p. 190–190.5°.

Anal. Calcd. for $C_{18}H_{14}O_3$: C, 77.7; H, 5.1. Found: C, 77.7; H, 5.0.

The methyl ether was prepared by the action of an excess of dimethyl sulfate on a solution of 100 mg. of the phenol from (b) above in 20 cc. of warm 10% potassium hydroxide. After evaporative distillation at 160–180° (0.2 mm.) and recrystallization from ethanol, nearly colorless needles were obtained with the m. p. 139–140°. A mixed melting point with the pure methyl ether prepared by direct cyclization was 139–140.5°.

3-(*p*-Hydroxyphenyl)-cyclopentanone-1 (VII). (a) By Reduction of the Unsaturated Phenol V.—A mixture of 526 mg. of the unsaturated phenol, 200 mg. of palladium-charcoal catalyst and 50 cc. of pure dioxane was shaken with hydrogen at room temperature and pressure. After eight hours an additional 200 mg. of catalyst was added and after fifteen hours one mole-equivalent of hydrogen had been absorbed. However, the product obtained upon removal of the catalyst and solvent was a mixture; by treatment with a small amount of benzene part of the material dissolved, leaving 100 mg. of unhydrogenated starting material, m. p. 225–231° (dec.). Crystallization of the benzene-soluble portion still led to mixtures, however, and the entire material was dissolved in alkali and benzoylated by means of excess benzoyl chloride. Two recrystallizations from ethanol gave 189 mg. (22%) of the benzoate of 3-(*p*-hydroxyphenyl)-cyclopentanone-1 with the m. p. 122.5–124.5°. After saponification by refluxing with 5% potassium hydroxide for one hour and several recrystallizations of the product from carbon tetrachloride the phenol was obtained with the m. p. 109–111°. A mixed melting point of this material with that obtained in (b) below showed no depression.

(b) By Demethylation of the Methyl Ether.—A solution of 174 mg. of the reduced methyl ether (m. p. 42–45.5°) in 5 cc. of acetic acid and 5 cc. of 42% hydrobromic acid was refluxed under a carbon dioxide atmosphere for two hours. The cooled mixture was extracted twice with ether and the phenolic material removed by washing with 5% sodium hydroxide. The alkaline layers were acidified and extracted with ether. Recrystallization of the residue from carbon tetrachloride (Norit) gave a total of 62 mg. (39%) of the phenol as colorless, cotton-like crystals with the m. p. 109–111°. After another recrystallization the m. p. of the compound was raised to 111–112°.

Anal.[13] Calcd. for $C_{11}H_{12}O_2$: C, 75.0; H, 6.9. Found: C, 74.5, 74.9; H, 7.0, 6.7.

The **benzoate**, prepared in 50% yield in dioxane–pyridine with benzoyl chloride, crystallized from ethanol as colorless blades with the m. p. 125–126°.

Anal.[13] Calcd. for $C_{18}H_{16}O_3$: C, 77.1; H, 5.7. Found: C, 76.9; 77.0; H, 5.9; 5.9.

Ethyl 5-(*p*-Methoxyphenyl)-2-methylfuran-3-carboxylate (VIII).—The crude *p*-methoxyphenacylacetoacetic

(13) Microanalysis by the Arlington Laboratories, Fairfax, Virginia.

ester prepared from 3.0 g. of *p*-methoxyphenacyl chloride as described above except not washed with alkali, was dissolved in 50 cc. of absolute alcohol, saturated with dry hydrogen chloride and refluxed for five hours. After evaporation of the ethanol the residue was dissolved in benzene and washed with dilute sodium hydroxide to remove a small amount of the acid (0.15 g.). The benzene solution was evaporated and the residue recrystallized from methanol, giving 1.95 g. of gray solid; m. p. 64–66°. Evaporative distillation of the filtrate at 140–160° (0.2 mm.) gave an additional 0.80 g. (m. p. 64–66°) bringing the total yield to 65%. The pure compound crystallized from methanol as colorless prisms, m. p. 66.0–67.0°. It gave a light-yellow color with sulfuric acid.

Anal. Calcd. for $C_{15}H_{16}O_4$: C, 69.2; H, 6.2. Found: C, 68.8; H, 6.3.

5-(*p*-Methoxyphenyl)-2-methylfuran-3-carboxylic Acid (IX).—A mixture of 6.0 g. of crude *p*-methoxyphenacylacetoacetic ester, prepared as described before, and 30 cc. of concentrated hydrochloric acid was refluxed for twenty hours, protected from air by means of a mercury trap. After cooling, the mixture was extracted with benzene and washed with water. The crude material, mainly the furan ester, was hydrolyzed by refluxing with 150 cc. of 5% potassium hydroxide for two hours. After extracting some neutral material, the aqueous layer was acidified and filtered. The product was then recrystallized from ethanol to give a total of 2.6 g. (52%) of the furan acid, m. p. 203–205°. Another recrystallization from ethanol raised the m. p. of the colorless prisms to 204.5–206°. The acid also was obtained in 93% yield by hydrolysis of the pure ethyl ester.

Anal. Calcd. for $C_{13}H_{12}O_4$: C, 67.2; H, 5.2. Found: C, 66.9; H, 5.3.

The neutral fraction from above, after evaporative distillation at 0.5 mm. and recrystallization from 90–100° petroleum ether, gave a small amount of 3-(*p*-methoxyphenyl)-cyclopenten-2-one-1, identified by m. p. and mixed m. p.

The methyl ester of the acid was prepared in 97% yield using ethereal diazomethane. The ester crystallized from methanol in colorless leaflets, m. p. 81.5–82°.

Anal. Calcd. for $C_{14}H_{14}O_4$: C, 68.3; H, 5.7. Found: C, 68.3; H, 5.8.

5-(*p*-Methoxyphenyl)-2-methylfuran (XI).—The furan acid (0.75 g.) was decarboxylated by refluxing for one and one-half hours with 15 cc. of quinoline and 0.3 g. of copper chromite catalyst. Benzene was then added and the mixture filtered. The benzene was washed thoroughly with dilute acid, alkali and water and the dark residue left after concentration was evaporatively distilled at 100–110° and 0.05 mm. to give 0.44 g. (72%) of the furan with the m. p. 42–44°. One recrystallization from dilute alcohol gave 0.36 g. with the m. p. 44–46°. The pure furan derivative was obtained by further recrystallization as hexagonal plates, m. p. 45.5–46°. The crystals gave a brown color with sulfuric acid and dissolved to give a yellow solution.

Anal. Calcd. for $C_{12}H_{12}O_2$: C, 76.6; H, 6.4. Found: C, 76.1; H, 6.4.

2-Hydroxy-3-acetyl-5-(*p*-methoxyphenyl)-furan (X).—A solution of 0.17 g. of sodium in 5 cc. of absolute alcohol was added to 2 g. of crude *p*-methoxyphenacylacetoacetic ester in 5 cc. of absolute alcohol. After five to ten minutes of gentle warming on the steam-bath, the mixture started to solidify. After twenty minutes the mixture was cooled, and the sodium salt filtered and washed with alcohol. The solid was dissolved in warm water, filtered and the solution acidified with dilute hydrochloric acid; 0.85 g. of crude product was obtained. Recrystallization of the material was accompanied by considerable loss. The compound existed in two polymorphic forms; recrystallization from methanol gave a buff-colored powder with the m. p. 126.5–129°, while recrystallization from 90–100° petroleum ether gave nearly colorless needles with the m. p. 100–102°. A mixture of the two forms melted at nearly the same point as the higher melting form. The analytical sample obtained by recrystallization from absolute ethanol had the m. p. 127–129°. The compound could be evaporatively distilled at 110–140° (0.3 mm.) without decomposition. It did undergo an undetermined type of decomposition upon standing for several weeks at room temperature. The compound gave an initial red-brown color with sulfuric acid, dissolving to a yellow solution; with alcoholic ferric chloride it gave a blue-green color.

Anal. Calcd. for $C_{13}H_{12}O_4$: C, 67.2; H, 5.2. Found: C, 67.5; H, 5.1.

Summary

The preparation of 3-(*p*-hydroxyphenyl)-cyclopenten-2-one-1 and its methyl ether was effected from the corresponding *p*-substituted phenacylacetoacetic esters by alkaline cyclization and hydrolysis. By reduction the related cyclopentanone derivatives were obtained.

The cyclization of *p*-methoxyphenacylacetoacetic ester to certain furan derivatives also was carried out.

MADISON, WISCONSIN RECEIVED OCTOBER 2, 1944

[CONTRIBUTION FROM THE STAMFORD RESEARCH LABORATORIES OF THE AMERICAN CYANAMID COMPANY]

Studies in Chemotherapy. VIII. Methionine and Purine Antagonists and their Relation to the Sulfonamides[1]

BY R. O. ROBLIN, JR., J. O. LAMPEN, J. P. ENGLISH, Q. P. COLE AND J. R. VAUGHAN, JR.

It has been suggested[2] that more potent *p*-aminobenzoic acid (PAB) antagonists are not likely to be found among sulfanilamide type compounds. On the other hand, an agent which interfered with another stage in PAB metabolism, when combined with sulfonamides, might be expected to enhance the effectiveness of the latter. Assuming that secondary sulfonamide inhibitors such as methionine[3] and the purines[4] may bear some metabolic relationship to PAB[3,4,5] we have attempted to prepare antagonists of these metabolites applying the general concept proposed by Fildes.[6]

(1) Presented in part before the Division of Medicinal Chemistry, New York meeting of the American Chemical Society, September 15, 1944.

(2) Bell and Roblin, THIS JOURNAL, 64, 2905 (1942).

(3) Bliss and Long, *Bull. Johns Hopkins Hosp.*, 69, 14 (1941); Harris and Kohn, *J. Pharmacol.*, 73, 383 (1941); Straus, Dingle and Finland, *J. Immunol.*, 43, 313, 331 (1941).

(4) Harris and Kohn, *J. Biol. Chem.*, 141, 989 (1941); Snell and Mitchell, *Arch. Biochem.*, 1, 93 (1942); Kohn and Harris, *J. Pharmacol.*, 77, 1 (1943).

(5) Kohn, *Ann. N. Y. Acad. Sci.*, 44, 503 (1943).

(6) Fildes, *Lancet, I*, 955 (1940); *cf.* Reviews by McIlwain, *Lancet, I*, 412 (1942); *Nature*, 151, 270 (1943); Kuhn, *Die Chemie*, 55, 1 (1942); Wagner-Jauregg, *Naturwissenschaften*, 31, 335 (1943).