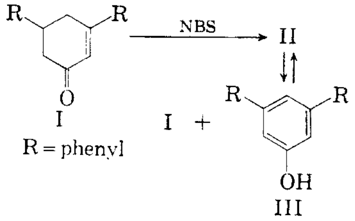
N-bromosuccinimide as the brominating agent might be more successful, as Deuschel reports that bromination of diethyl 2-oxo-4,6-diphenyl-6-cyclohexene-1,3-dicarboxylate with N-bromosuccinimide gives the corresponding phenol in excellent yield.



3,5 - Diphenyl - 2 - cyclohexen - 1 - one was prepared by the condensation of benzalacetophenone and acetoacetic ester, followed by hydrolysis and decarboxylation.[4] Bromination was readily effected with N-bromosuccinimide and the bromo-3,5-diphenyl-2-cyclohexen-1-one lost hydrogen bromide spontaneously. Recrystallization of the product gave 85–90% yields of a compound (II), m.p. 123–124°. The infrared spectrum indicated bonded hydroxyl (3300 cm.$^{-1}$) and conjugated carbonyl (1645 cm.$^{-1}$). The compound gave analysis corresponding to $C_{36}H_{30}O_2$.

Compound II proved to be an equimolar complex of 3,5-diphenylphenol (m.p. 94°[3]) and 3,5-diphenyl-2-cyclohexen-1-one (m.p. 82,[1] 89°[5]), and was also prepared by recrystallizing a mixture of I and III from hexane or ethanol. Compound formation was demonstrated by the method of Kofler[6] using a hot stage microscope. By heating a slide covered half by the phenol and half by the ketone, melting was observed at 85° and 92° corresponding to the two eutectics, at 89° and 94° for the two pure components, and at 124° for the compound, II.

The solution characteristics of II indicate essentially complete dissociation in dilute solution. The molecular weight, by cryoscopic or ebullioscopic methods, is 246 (theor. 246). The ultraviolet spectrum of II, in ethanol, is equal to the sum of the spectra of its two components. The strongly bonded hydroxyl frequency shifts to shorter wave lengths on dilution in chloroform as would be expected if dissociation occurred. Compound II may be separated into its components by extraction of the phenol from a solution of II in benzene-petroleum ether with Claisen's alkali or by chromatography on Woelm acid alumina grade one. The components may also be separated by the preparation of ketone (2,4-dinitrophenylhydrazone) or hydroxyl (methyl ether) derivatives. The overall yield of the phenol, using the alkali separation, based on I is 75–80%, allowing for recovered ketone. The recovered starting material from the complex may be recycled without further purification.

Apparently the spontaneous dehydrobromination begins when the bromination approaches 40–50% completion and the evolved hydrogen bromide halts further bromination. To circumvent this problem and increase the yield of III, large excesses of N-bromosuccinimide and peroxide catalyst were used. In these cases, the overall yield of II was reduced from 90% to 70–80% and some excess phenol was produced.

EXPERIMENTAL

3,5-Diphenyl-2-cyclohexen-1-one (I). Ethyl 4,6-diphenyl-2-oxo-3-cyclohexenecarboxylate[4] (9.0 g.) was dissolved in 50 ml. methanol and 50 ml. 10% aqueous sodium hydroxide was added. The solution was refluxed for 2 hr., cooled, and acidified with hydrochloric acid. Carbon dioxide was vigorously evolved. The solution was refluxed for 2 hr. and then concentrated. White crystals separated and were collected and dried. The product was recrystallized from ethanol giving 5.2 g. of I (85%) m.p. 82°.

Compound of 3,5-diphenylphenol and 3,5-diphenyl-2-cyclohexen-1-one (II). 3,5-Diphenyl-2-cyclohexen-1-one (2.0 g.) was dissolved in 25 ml. dry carbon tetrachloride by warming. To the solution was added 1.42 g. N-bromosuccinimide. The mixture was refluxed for 3 hr., during which time a red color developed. At the end of this time the reaction turned pale yellow and hydrogen bromide was evolved. After 1 hr additional refluxing the mixture was cooled and filtered to remove the succinimide. The carbon tetrachloride solution was then evaporated to dryness, leaving 2.0 g. reddish crystals, m.p. 95–98°. The product was recrystallized from hexane giving 1.75 g. (87% of theor.) of white crystals m.p. 123–124°.

A small sample recrystallized several times for analysis melted at 123.5–124.5°.

Anal. Calcd. for $C_{36}H_{30}O_2$: C, 87.42; H, 6.11. Found: C, 87.46; H, 6.16.

3,5-Diphenylphenol (III). Compound II (300 mg.) was dissolved in a mixture of 10 ml. benzene and 20 ml. petroleum ether. The solution was extracted with three 10-ml. portions of Claisen's alkali. The extract was diluted with an equal volume of water and acidified with hydrochloric acid. A tan oil separated which solidified on standing. The solid was collected and recrystallized from hexane (135 mg., m.p. 93–94°). Evaporation of the benzene-petroleum ether solution to dryness gave 150 mg. of a tan oil which crystallized from hexane giving 130 mg. I, m.p. 82–83°.

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[4] E. Knoevenagel, *Ann.*, **281**, 59 (1894).

[5] W. Dieckmann, and K. von Fischer, *Ber.*, **44**, 971 (1911).

[6] A. Kofler, *Z. physik. Chem.*, A 187, 201 (1940); A. Kofler, *Z. physik. Chem.*, 363 (1940).

Preparation of Certain 4-Acylphenols[1]

Robert A. Bragole and Robert A. Shepard

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A number of 4-acylphenols have been synthesized in conjunction with a study of ionization constants:

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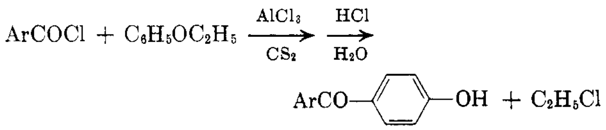
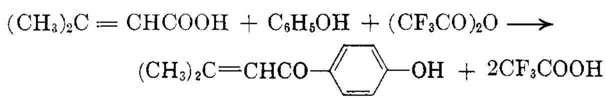
[1] From the M. S. thesis research of R. A. Bragole.



I. Ar = 3-$CH_3C_6H_4$
II. Ar = 3-$CH_3OC_6H_4$
III. Ar = 3-$CF_3C_6H_4$
IV. Ar = 3,4-$Cl_2C_6H_3$
V. Ar = 3,5-$(NO_2)_2C_6H_3$



VI

Three acylation methods were attempted: (a) polyphosphoric acid condensation of phenol with a carboxylic acid,[2] (b) trifluoroacetic anhydride condensation of phenol with a carboxylic acid,[3] and (c) Friedel-Crafts acylation of phenetole.[4] The last of these methods was the most generally successful in these preparations, giving the best yields of compounds I through V. Compound VI was synthesized by the trifluoroacetic anhydride condensation, but it could also be prepared by the Friedel-Crafts reaction, although in poorer yield. Phenyl esters ($C_6H_5OCOC_6H_4R$) rather than acylphenols were formed during the attempted synthesis of compounds I and II by trifluoroacetic anhydride condensation. Polyphosphoric acid condensation was ineffective for these particular compounds (I–VI), although some acylphenols have been prepared by this method, notably I in 19% yield and II in 15% yield.[2b] None of the products, I–VI, was accompanied by the isomeric 2-acylphenol, but in the course of preparing the known 3-nitro-4′-hydroxybenzophenone some of the 2-acylphenol, as its aluminum chelate, precipitated with the desired product when the Friedel-Crafts reaction mixture was hydrolyzed. Such chelates of 2-acylphenols have been reported earlier.[5] The aluminum chelate was insoluble in alkali and dilute acid but was decomposed by cold concentrated sulfuric acid to release the free 3-nitro-2′-hydroxybenzophenone.[6] This 2-acylphenol behaves much like salicylaldehyde and *o*-hydroxyacetophenone, which displace ammonia from the blue tetramminenickel ion to yield pale yellow or pale green solutions, from which stable nickel chelates may be isolated.[5] The 4-acylphenols have no visible effect upon solutions of tetramminenickel ion.

EXPERIMENTAL

3-Methyl-4′-hydroxybenzophenone (I). Phenetole (4.64 g., 0.038 mole) and aluminum chloride (15.3 g., 0.115 mole) in 165 cc. of carbon disulfide were stirred together for 0.5 hr. at 0–5°. A solution of 6.05 g. (0.039 mole) *m*-toluoyl chloride in 45 cc. of carbon disulfide was added at 0–5° over a 0.5-hr. period with subsequent stirring for 7.5 hr. The mixture was left to stand at room temperature overnight. Upon treating the mixture with ice and hydrochloric acid, a white precipitate consisting largely of the desired 4-acylphenol was obtained. This was dissolved in 10% sodium hydroxide, and the solution treated with activated charcoal and filtered. The product, reprecipitated by acidifying the solution, was collected, washed with sodium bicarbonate to remove any *m*-toluic acid, washed again with water, and dried under vacuum. The yield was 4 g. (50%): m.p. 163–164°. Nakazawa and Baba report m.p. 166°.[2b] Extraction of the carbon disulfide layer with 10% sodium hydroxide yielded a negligible amount of precipitate on acidification of the aqueous layer. A small amount of red oil remained after distillation of the carbon disulfide, but it could not be crystallized.

Anal. Calcd. for $C_{14}H_{12}O_2$: C, 79.2; H, 5.7. Found: C, 79.0; H, 5.6.

3-Methoxy-4′-hydroxybenzophenone (II) was prepared in 51% yield by the same experimental method as I; m.p. 141–142°. Nakazawa and Baba report m.p. 138°.[2b]

Anal. Calcd. for $C_{14}H_{12}O_3$: C, 73.7; H, 5.3. Found: C, 73.6; H, 5.4.

3-Trifluoromethyl-4′-hydroxybenzophenone (III) was prepared in 21% yield by an experimental method similar to that used for I; m.p. 144–145°.

Anal. Calcd. for $C_{14}H_9F_3O_2$: F, 21.4. Found: F, 21.3.

3,4-Dichloro-4′-hydroxybenzophenone (IV) was prepared in 40% yield by the same experimental method as I; m.p. 172–174°.

Anal. Calcd. for $C_{13}H_8Cl_2O_2$: Cl, 26.6. Found: Cl, 26.6.

The carbon disulfide residue yielded 3 g. of red solid, m.p. 72–74°. This is most probably 3,4-dichloro-4′-ethoxybenzophenone, for treatment with aluminum chloride in refluxing carbon disulfide, followed by hydrolysis, converted it to the free phenol IV.

3,5-Dinitro-4′-hydroxybenzophenone (V) was prepared in 60% yield by the same experimental method as I; m.p. 196–197° dec.

Anal. Calcd. for $C_{13}H_8N_2O_6$: N, 9.7. Found: N, 9.8.

p-Hydroxyseneciophenone (VI). Senecioic acid (10 g., 0.1 mole) was dissolved in 42 cc. of trifluoroacetic anhydride. Phenol (10.8 g., 0.115 mole) was added, and the resulting mixture was refluxed gently for 4 hr. The mixture was allowed to stand 120 hr. at room temperature and then poured slowly with stirring into excess 10% aqueous sodium bicarbonate. When effervescence subsided, the mixture was extracted with several small portions of ether and the combined ether extract was dried over magnesium sulfate. After the ether was removed, the remaining oil was distilled twice at reduced pressure. The weight of the colorless oil which upon chilling froze to long needles was 9.15 g. (52%); b.p. 96° (12 mm.), m.p. 28–29°.

Anal. Calcd. for $C_{11}H_{12}O_2$: C, 75.0; H, 6.8. Found: C, 74.7; H, 7.0.

p-Hydroxyseneciophenone has the effect of a potent local anesthetic. Approximately 10 min. after contact of a drop of the oil with the skin, one begins to feel a numbing sensation at the area of contact. Addition of water to the area of contact seems to promote a striking insensitivity to pain (pin-pricks, hot surfaces, etc.) at the area of contact for a duration of 3 hr. or more, after which complete feeling is restored without any other noticeable effects.

Chelates of 3-nitro-2′-hydroxybenzophenone. The aluminum chelate of 3-nitro-2′-hydroxybenzophenone was isolated during the preparation of 3-nitro-4′-hydroxybenzophenone by a Friedel-Crafts acylation. Upon treating the reaction

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(2) (a) H. R. Snyder and C. T. Elston, *J. Am. Chem. Soc.*, **77**, 364 (1955); (b) K. Nakazawa and S. Baba, *J. Pharm. Soc. Japan*, **75**, 378 (1955); *Chem. Abstr.* **50**, 2510c (1956).

(3) E. J. Bourne, M. Stacey, J. C. Tatlow, and J. M. Tedder, *J. Chem. Soc.*, **1951**, 718.

(4) P. J. Montagne, *Rec. trav. chim.*, **39**, 339 (1920).

(5) A. E. Martell and M. Calvin, *Chemistry of Metal Chelates*, Prentice-Hall, Inc., 1956, pp. 184, 185, 216, 228, 423.

(6) D. F. DeTar and D. I. Relyea, *J. Am. Chem. Soc.*, **76**, 1680 (1954).

mixture with ice and concd. hydrochloric acid, the aluminum complex and the free 4-acylphenol precipitated together. The complex was separated from the 4-acylphenol by treating the mixture with aqueous sodium hydroxide. The complex was decomposed with cold concd. sulfuric acid, and the free 2-acylphenol precipitated upon dilution with water. The aqueous filtrate gave a positive test for the aluminum ion. Upon treating the free 2-acylphenol with alcoholic tetramminenickel (II) chloride solution, a yellow solution resulted. Evaporation of most of the alcohol resulted in the precipitation of the stable nickel chelate, which was pale yellow. There was a striking resemblance of this chelate to that of the known nickel chelate of *o*-hydroxyacetophenone.[3] Treatment of this chelate with cold concd. sulfuric acid released the original 2-acylphenol upon dilution with water. The aqueous filtrate gave a positive test for the nickel ion.

Anal. Calcd. for $(C_{13}H_8O_4N)_2Ni$: Ni, 10.81. Found: Ni, 10.82.

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Condensation of Triethyl Phosphonoacetate with Aromatic Aldehydes

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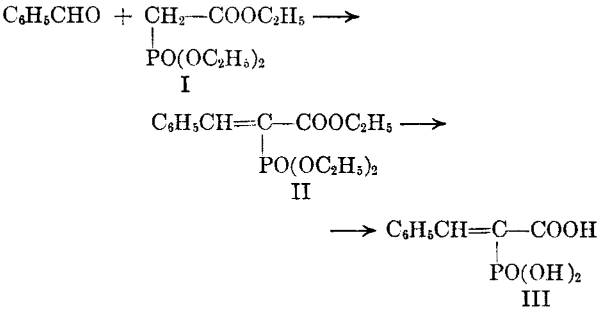
Our interest was attracted by a communication in which benzaldehyde and triethyl phosphonoacetate (I), on heating at 160–170° with acetic anhydride was reported to give triethylbenzylidenephosphonoacetate (II) yielding on acid hydrolysis what was claimed to be the benzylidene phosphonoacetic acid (III).[1]

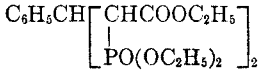


$$C_6H_5CHO + \underset{\underset{\text{I}}{PO(OC_2H_5)_2}}{\underset{|}{CH_2}}{-}COOC_2H_5 \longrightarrow C_6H_5CH{=}\underset{\underset{\text{II}}{PO(OC_2H_5)_2}}{\underset{|}{C}}{-}COOC_2H_5 \longrightarrow C_6H_5CH{=}\underset{\underset{\text{III}}{PO(OH)_2}}{\underset{|}{C}}{-}COOH$$

In view of the instability of the arylidenemalonic acids, which lose carbon dioxide rather easily both under acidic and basic conditions, the preparation of benzylidene phosphonoacetic acid by acid hydrolysis of the corresponding triester was somewhat surprising, and as no experimental details or analysis of the final product are given in Pudovik and Lebedeva's paper, we decided to re-investigate this reaction.

Under the conditions of the Russian authors, which are essentially those of the Perkin reaction, we obtained about 12% of a product, which gave on hydrolysis cinnamic acid, while 83–85% of the aldehyde could be recovered unchanged. The physical constants of the primary condensation product obtained by us, as well as its carbon-hydrogen analysis were in reasonable agreement with that obtained by the Russian authors, although the yield was very much smaller than claimed by them. On the other hand, we were unable to obtain by the hydrolysis of the triester any other product but cinnamic acid (which was identified by melting point, mixed melting point, analysis, and melting point of its bromophenacyl bromide derivative), although widely varied concentrations of both hydrochloric acid and potassium hydroxide were employed in various experiments. Indeed, the acid obtained by Pudovik and Lebedeva was stated by them to have a melting point of 132°, which is practically identical with that of cinnamic acid, and we believe that it actually was cinnamic acid. As no analysis is given in their paper, it may well be that this was identified as benzylidenephosphonoacetic solely on the assumption that hydrolysis of the triester must give the corresponding tribasic acid, without the occurrence of any further reaction.

Using different reaction techniques and basic catalysts, we were able to obtain much better yields of the triethylbenzylidenephosphonoacetate. (See Table I.) Incidentally, by careful fractionation of the reaction product obtained in the ethanol-piperidine mixture, an additional substance could be obtained, which gave the correct analysis for benzylidene bis(triethyl phosphonoacetate) IV, i.e., the condensation product of one mole of



$$C_6H_5CH\left[\begin{array}{l}CHCOOC_2H_5\\ |\\ PO(OC_2H_5)_2\end{array}\right]_2$$

IV

benzaldehyde with two moles of triethyl phosphonoacetate. This product, too, gave cinnamic acid on hydrolysis, and its formation is analogous to the formation of a similar condensation product from two moles of ethyl nitroacetate and one mole of benzaldehyde.[2]

In similar experiments, with *p*-nitrobenzaldehyde and triethyl phosphonoacetate in ethanol as solvent and piperidine as the catalyst, very high yields (83%) of ethyl *p*-nitrocinnamate were obtained. No phosphorus-containing product could be isolated from the reaction mixture.

The relative strength of carbon-carbon and carbon-phosphorus bonds. The strength of carbon-carbon and carbon-phosphorus bonds, other things being equal, is of about the same order.[3]

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(1) A. N. Pudovik and N. M. Lebedeva, *Doklady Akad. Nauk S.S.S.R.*, **90**, 799 (1953) [*Chem. Abstr.*, **50**, 2429^d (1956)], names the final product (III) erroneously benzylidene phosphonic acid instead of benzylidene phosphonoacetic acid, as in the Russian text.

(2) A. D. Dornow and G. Wiehler, *Ann.* **578**, 117 (1952).

(3) For a review of recent literature see P. C. Crofts, *Quart. Rev.* **12**, 341 (1958), and papers quoted there.