[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF ROCHESTER]

Use of Mixed Carboxylic-Carbonic Anhydrides for Acylations on Carbon and Oxygen[1]

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Mixed carboxylic-carbonic anhydrides, prepared from carboxylic acids, triethylamine and alkyl chlorocarbonates in an inert solvent at 0°, have been found to acylate diethyl malonate and diethyl ethylmalonate, at room temperature or below, in satisfactory yields. The compounds prepared by this procedure include diethyl benzoylmalonate (V, 68–75%), diethyl acetylmalonate (VI, 54%), diethyl benzoylethylmalonate (VII, 17%) and diethyl (acetylsalicyloyl)-malonate (VIII), identified by conversion to 3-carbethoxy-4-hydroxycoumarin in 45% over-all yield. Benzoic-carbonic anhydride and diethyl cadmium give a 60% yield of propiophenone. Diazoacetophenone and diazomethyl isobutyl ketone are obtained from the corresponding mixed anhydrides and diazomethane. Low yields of 3,4-dimethoxybenzophenone have been obtained from the Friedel-Crafts reaction between the mixed benzoic anhydride and veratrole. This reaction has been shown to involve the mixed anhydride, and not other possible derived compounds, as the reactive intermediate. Phenols have been acylated by the mixed anhydrides. The acylation of alcohols by the mixed anhydrides to form carboxylic esters gives poor yields in general. The mixed anhydride from benzoic acid and 2,4-dimethylpentanol-3 chlorocarbonate yields mainly the benzoate of 2,4-dimethylpentanol-3 in the presence of ethanol and isoamyl alcohol indicating that the mixed anhydride probably undergoes an intramolecular reaction with alkyl-oxygen cleavage of the highly branched alkyl group. The mixed anhydrides appear to be useful reagents for acylation of active methylene groups, of organocadmium compounds, of phenols, of diazomethane, and possibly in some cases of alcohols; the essentially neutral conditions under which they are prepared, and the mild conditions under which they react, may make them the reagent of choice in dealing with acid-sensitive compounds.

In connection with some projected synthetic sequences, we wished to know if the mixed carbonic anhydride procedure,[3] which has proved so useful for the synthesis of amide linkages,[4,5] could be employed for the acylation of malonic esters. The fact that the mixed carboxylic-carbonic anhydrides can be prepared at 0° under essentially neutral conditions, and that they acylate amines under the same mild conditions, made a survey of their reactions with nucleophilic types other than amines a desirable problem. It appears, from the results reported below, that the mixed anhydrides may be used successfully to acylate malonic esters, to prepare ketones from organocadmium compounds, to acylate phenols, and to prepare diazoketones from diazomethane. The use of the mixed anhydrides in the Friedel-Crafts ketone synthesis and in the acylation of alcohols to form carboxylic esters, appears to be less promising as a general synthetic procedure, although both reactions have been shown to take place.

The mixed anhydrides were prepared[3,4] by the action of triethylamine and ethyl chlorocarbonate[6] on the carboxylic acid in ether or preferably in toluene at 0°, according to the following equation

$$\mathrm{RCOOH + ClCOOEt + Et_3N \longrightarrow RCO{-}O{-}CO{-}OEt + Et_3N{:}HCl}$$

$$\text{I, R} = \mathrm{C_6H_5}$$
$$\text{II, R} = \mathrm{CH_3}$$

Most of the acylations of malonic esters were carried out on the magnesium ethoxy derivatives,[7] which are reported[8] to have some advantages over the sodio derivatives.[9] The magnesium ethoxy compounds in dry ether were added, at −5° to 0°, to the mixed anhydride. The mixture was allowed to come to room temperature overnight, and was then worked up. By this procedure, diethyl benzoylmalonate (V) and diethyl acetylmalonate (VI) were obtained, and the hitherto undescribed diethyl benzoylethylmalonate (VII) was prepared in 17% yield.

$$\mathrm{RCOOCOOEt + EtOMgCR'(COOEt)_2 \longrightarrow RCO{-}CR'(COOEt)_2}$$

$$\text{III, R}' = \mathrm{H}$$
$$\text{IV, R}' = \mathrm{C_2H_5}$$
$$\text{V, R} = \mathrm{C_6H_5},\ \text{R}' = \mathrm{H}$$
$$\text{VI, R} = \mathrm{CH_3},\ \text{R}' = \mathrm{H}$$
$$\text{VII, R} = \mathrm{C_6H_5},\ \text{R}' = \mathrm{C_2H_5}$$

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(1) Part of this material has been presented in a preliminary report [D. S. Tarbell and J. A. Price, *J. Org. Chem.*, 21, 144 (1956)].

(2) Abbott Laboratories Fellow, 1955–56.

(3) J. R. Vaughan, Jr., *J. Am. Chem. Soc.*, **73**, 3547 (1951); R. A. Boissonnas, *Helv. Chim. Acta*, **34**, 874 (1951); T. Wieland and H. Bernhard, *Ann.*, **572**, 190 (1951).

(4) *E.g.*, J. R. Vaughan, Jr., and R. L. Osato, *J. Am. Chem. Soc.*, **73**, 5553 (1951); **74**, 676 (1952); J. R. Vaughan, Jr., and J. A. Eichler, *J. Am. Chem. Soc.*, **75**, 5556 (1953); **76**, 2474 (1954); V. du Vigneaud *et al.*, *J. Am. Chem. Soc.*, **75**, 4879 (1953); **76**, 3107 (1954); B. R. Baker *et al.*, *J. Org. Chem.*, **19**, 1786 (1954).

(5) Acylation of thiophenols by the mixed carbonic anhydride procedure is reported by T. Wieland, W. Schäfer, and E. Bokelmann, *Ann.*, **573**, 99 (1951).

(6) Other chlorocarbonates may be used, but the ethyl ester is preferable in working with diethyl malonates, to prevent complications due to ester interchange reactions.

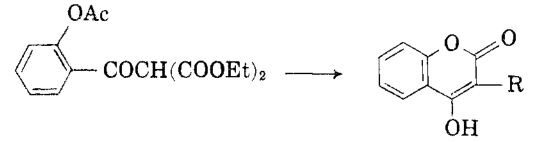
(7) H. Lund, *Ber.*, **67**, 935 (1934); *Org. Syntheses*, **Coll. Vol. II**, 594 (1943).

(8) H. Lund, A. U. Hansen, and A. F. Voigt, *Kgl. Danske Videnskab. Selskab. Mat.-fys. Medd.*, **12**, No. 9 (1933); [*Chem. Abstr.*, **28**, 2333 (1934)].

(9) One trial of sodiomalonic ester and benzoic-carbonic anhydride gave an unsatisfactory yield in our hands; the sodio derivative forms a very viscous solution in ether-toluene, which is not easily manipulated. The magnesium ethoxy derivative is more soluble and is more readily handled, although its preparation is more laborious.

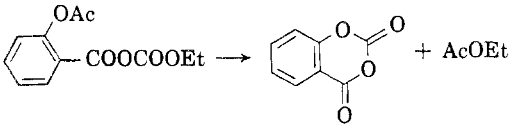
It was not necessary to remove the precipitated triethylamine hydrochloride before the acylation of the malonates; the salt is evidently too insoluble in the reaction mixture to affect the reaction.

The yield of acylmalonates from a monosubstituted malonic ester by other methods appears to be uniformly low[10,11]; in the present case, there was a considerable forerun, which appeared, from its analysis and infrared spectrum, to be a mixture of starting material and some of the possible cleavage products.[12] The acylalkylmalonate VII was cleaved to benzoic acid by standing for several months at room temperature; both V and VII were split rapidly by phenylhydrazine, giving β-benzoylphenylhydrazine. This high rate of cleavage of the acyl group is in accord with previous experience.[10,13] The attempted acylation of III by the mixed anhydride prepared from salicylic acid was unsatisfactory; there appeared to be some dimer formed,[14] because heating the anhydride or hydrolysis with water did not regenerate all of the salicylic acid. However, acetylsalicylic acid was converted to the mixed anhydride and was allowed to react with the enolate III in the usual way; the product, presumably VIII, cyclized to



VIII IX, R = COOEt
X, R = H

3-carbethoxy-4-hydroxycoumarin on distillation.[15] The conversion was also brought about, in 45% over-all yield from acetylsalicylic acid, by 10% alkali in the cold. The carbethoxycoumarin IX was hydrolyzed and decarboxylated to yield 4-hydroxycoumarin (X); IX was identified by mixed melting point with an authentic sample of this compound,[16] and X was condensed with formaldehyde to yield 3,3′-methylenebis(4-hydroxycoumarin).[17] A possible intermediate in the acylation by the mixed anhydride from acetylsalicyclic acid (XI) would be the

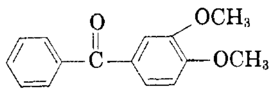


XI XII

cyclic anhydride XII[18]; this compound was prepared, and it did not acylate the malonate derivative in yields at all comparable to those obtained with the mixed anhydride XI. This observation, as well as those of Ghosh,[15] indicate that XII is not an intermediate in the acylation.

It was found that the benzoic-carbonic anhydride I and diethyl cadmium[19] gave a 60% yield of propiophenone; presumably this reaction is general. In the reaction of the mixed anhydride with the diethyl cadmium, it is necessary to remove the triethylamine hydrochloride from the mixed anhydride by filtration, before the mixed anhydride is added to the dialkyl cadmium solution. If this is not done, the amine salt appears to decompose the cadmium compound more rapidly than the mixed anhydride reacts with the cadmium compound, and no ketone is obtained.

Davies[18] showed that the cyclic anhydride XII, and the corresponding one derived from glycolic acid, gave good yields in the Friedel-Crafts reaction with benzene and aluminum chloride. We have obtained a maximum of 17% of 3,4-dimethoxybenzophenone (XIII) by the action of the benzoic-carbonic anhydride I on veratrole with aluminum chloride at 0° with carbon disulfide as solvent. With stannic chloride as catalyst, 11% of the ketone was obtained. Treatment of veratrole with the mixed anhydride I and perchloric acid[20] yielded no ketone.



XIII

It was possible that the ketone XIII actually obtained in the acylations using the benzoic-carbonic anhydride I might have been due to the intermediate formation, from the mixed anhydride, of ethyl benzoate, benzoic acid, or benzoic anhydride, which then acted as acylating agents. However, separate trials of each of these three compounds under the conditions used for the mixed anhydride acylations, failed to yield detectable amounts of

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(10) R. Meyer and H. Lüders, *Ann.*, **415**, 43 (1918).

(11) W. S. Johnson and R. D. Offenhauer, *J. Am. Chem. Soc.*, **67**, 1045 (1945); H. G. Walker and C. R. Hauser, *J. Am. Chem. Soc.*, **68**, 1386 (1946).

(12) *Cf.* A. C. Cope and S. M. McElvain, *J. Am. Chem. Soc.*, **54**, 4311 (1932) for the cleavage of malonates by sodium ethoxide.

(13) W. Borsche and U. Wannagat, *Ber.*, **85**, 193 (1952).

(14) *Cf.* W. Baker, W. D. Ollis, and T. S. Zealley, *J. Chem. Soc.*, 201 (1951).

(15) K. C. Ghosh, *J. Indian Chem. Soc.*, **24**, 321 (1947), reported that acetylsalicyloyl chloride and methylmalonic ester yield o-$C_6H_4(OAc)COC(CH_3)(COOEt)_2$ which distills at 198° (4 mm.); it was cyclized to 3-methyl-4-hydroxycoumarin by dilute sulfuric acid.

(16) M. E. Hultquist, U. S. Patent **2,449,038** [*C. A.*, **43**, 693 (1949)]; R. Anschutz, *Ann.*, **367**, 174 (1909).

(17) M. A. Stahmann, C. F. Huebner, and K. P. Link, *J. Biol. Chem.*, **138**, 513 (1941).

(18) L. A. Dupont, French Patent **771,653** [*C. A.*, **29**, 816 (1935)]; A. E. Chichibabin, *Compt. rend.*, **213**, 355 (1941); W. H. Davies, *J. Chem. Soc.*, 1357 (1951).

(19) H. Gilman and J. F. Nelson, *Rec. trav. chim.*, **55**, 518 (1936); for reviews of the preparation of ketones from acid chlorides and organometallic compounds, see J. Cason, *Chem. Revs.*, **40**, 15 (1947); D. A. Shirley, *Org. Reactions*, VIII, 28–58 (1954).

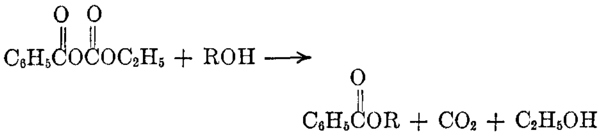
(20) H. Burton and P. F. G. Praill, *J. Chem. Soc.*, 529 (1951), obtained Friedel-Crafts acylations with carboxylic anhydrides and aqueous perchloric acid as catalyst.

the ketone. Hence it appears that the mixed anhydride is the acylating agent.

Attempts to acylate furan with the mixed anhydride I and an iodine catalyst[21] were unsuccessful. The reaction of benzoic-carbonic anhydride with ethereal diazomethane yielded a small amount of pure diazoacetophenone; the low yield apparently due to difficulties in isolation of the low melting solid. The action of diazomethane on the mixed isovaleric-carbonic anhydride, $(CH_3)_2CHCH_2COO$-$COOEt$, gave a 57% yield of the corresponding diazoketone. This reaction should be useful synthetically. In these reactions, the triethylamine hydrochloride was separated before the addition to diazomethane.

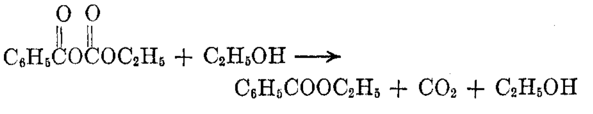
The usefulness of the mixed anhydrides for acylation of phenols and alcohols was investigated in several cases. The benzoylation of phenol by the benzoic-carbonic anhydride I have a poor yield of the low-melting phenyl benzoate; 4-phenylphenyl benzoate was obtained in 54% yield of recrystallized material from 4-phenylphenol. Benzyl benzoate was obtained in 47% yield from the benzoic-carbonic anhydride I and benzyl alcohol.

Benzoylation of isoamyl alcohol by the anhydride I gave 25% of isoamyl benzoate, and there was some evidence for the formation of benzoic anhydride and ethyl benzoate. The reaction involved in the acylation of an alcohol by the anhydride I would be

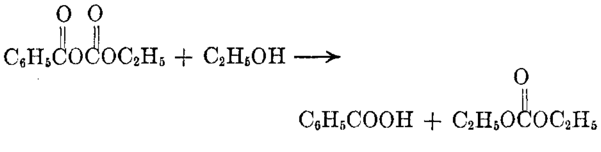


$$C_6H_5\overset{O}{\overset{\|}{C}}O\overset{O}{\overset{\|}{C}}OC_2H_5 + ROH \longrightarrow C_6H_5\overset{O}{\overset{\|}{C}}OR + CO_2 + C_2H_5OH$$

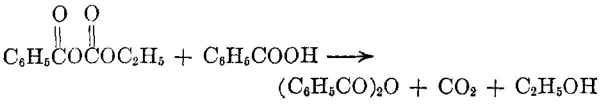
The C_2H_5OH liberated might react with unchanged mixed anhydride in several ways, some of which follow



$$C_6H_5\overset{O}{\overset{\|}{C}}O\overset{O}{\overset{\|}{C}}OC_2H_5 + C_2H_5OH \longrightarrow C_6H_5COOC_2H_5 + CO_2 + C_2H_5OH$$

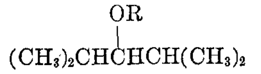


$$C_6H_5\overset{O}{\overset{\|}{C}}O\overset{O}{\overset{\|}{C}}OC_2H_5 + C_2H_5OH \longrightarrow C_6H_5COOH + C_2H_5O\overset{O}{\overset{\|}{C}}OC_2H_5$$



$$C_6H_5\overset{O}{\overset{\|}{C}}O\overset{O}{\overset{\|}{C}}OC_2H_5 + C_6H_5COOH \longrightarrow (C_6H_5CO)_2O + CO_2 + C_2H_5OH$$

It seemed that these unwanted side reactions might be prevented by using as the alcohol component of the mixed anhydride a highly branched alcohol such as 2,4-dimethylpentanol-3 (XIV). It is known from the work of Norris[22] that the rate of acylation of alcohols is decreased greatly by increasing substitution, and one might predict that XIV would react with acylating agents at a rate smaller than that of ethanol by a factor of at least 10^2.

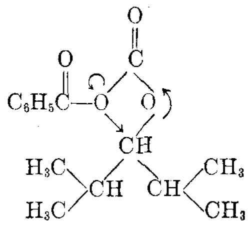


$$(CH_3)_2CH\overset{OR}{\overset{|}{C}}HCH(CH_3)_2$$

XIV, R = H
XV, R = COCl
XVI, R = $CONH_2$
XVII, R = C_6H_5CO

2,4-Dimethylpentanol-3 was prepared readily by lithium aluminum hydride reduction of diisopropyl ketone,[23] and was converted to the chlorocarbonate XV by phosgene; this compound was also characterized as the solid carbamate XVI.

The mixed benzoic-carbonic anhydride prepared from the highly branched chlorocarbonate XV was treated with ethyl alcohol; the products were ethyl benzoate (13%) and 2,4-dimethylpentanol-3 benzoate (XVII, 49%). It is highly unlikely that this ester can have resulted from reaction of the liberated dimethylpentanol with unchanged anhydride, in competition with ethanol; it seems probable that the branched chain ester results from an intramolecular reaction of the S_{Ni} type, with the transition state shown below, involving alkyl-oxygen cleavage. Examination of models shows that this four membered cyclic transition state is possible on steric grounds. This reaction is being investigated further.



The mixed anhydride procedure does not therefore appear at present to be a promising one for the acylation of alcoholic hydroxyl groups.

EXPERIMENTAL[24]

DIETHYL BENZOYLMALONATE (V)

A. *Magnesium ethoxy malonic ester.*[7,25] Magnesium turnings (5.0 g.), 5 cc. of commercial absolute alcohol, 0.2 cc. of carbon tetrachloride, and 6 cc. of a mixture of 32.0 g

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[21] *Cf.* H. D. Hartough and A. I. Kosak, *J. Am. Chem. Soc.*, **68**, 2639 (1946).

[22] J. F. Norris and A. A. Ashdown, *J. Am. Chem. Soc.*, **47**, 837 (1925); J. F. Norris and F. Cortese, *J. Am. Chem. Soc.*, **49**, 2640 (1927).

[23] J. B. Conant and A. H. Blatt, *J. Am. Chem. Soc.*, **51**, 1227 (1929), showed that this ketone was reduced to the secondary alcohol by Grignard reagents.

[24] Analyses are by Miss Annette Smith and Microtech Laboratories. Yields are based on starting material taken and do not take into account any recovered starting material.

[25] *Cf.* G. A. Reynolds and C. R. Hauser, *Org. Syntheses*, **30**, 70 (1950).

of diethyl malonate (redistilled n_{D}^{20} 1.4047) and 16 cc. of absolute alcohol are placed in a flask equipped with a dropping funnel and a reflux condenser protected by a calcium chloride tube. The reaction starts spontaneously and may require occasional cooling; the remainder of the diethyl malonate is added at a rate sufficient to maintain a vigorous reaction. When the reaction has cooled to room temperature, 60 cc. of dry ether is added cautiously; the ether dissolves the cake of magnesium ethoxy derivative, and a vigorous reaction starts with unchanged magnesium. When the reaction has subsided, the mixture is heated on the steam bath until nearly all of the magnesium has dissolved; this requires 6–8 hr. The alcohol and ether are removed by distillation first at atmospheric pressure, then with the water pump. Dry benzene (60 cc.) is added to the residue, and the solvent is then removed as before. The residue is dissolved in 60 cc. of dry ether.

B. Benzoic-carbonic anhydride (I). A solution of 24.4 g. of benzoic acid and 20.2 g. of triethylamine in 200 cc. of dry toluene is placed in a three-necked flask fitted with a stirrer, a low temperature thermometer, and a dropping funnel protected by a drying tube. The solution is cooled below 0° with an ice-salt mixture, and 21.7 g. of redistilled ethyl chlorocarbonate is added at such a rate that the temperature does not rise above 0°; this requires 25–30 min. Triethylamine hydrochloride precipitates during both the addition and a subsequent period of stirring for 15–25 min.

C. Acylation reaction. The dropping funnel used for the chlorocarbonate addition is replaced by another containing the ethereal solution of the ethoxy magnesium malonate. The ether solution is added to the mixed anhydride with stirring, keeping the temperature at −5°–0°. The mixture is allowed to stand overnight and to come to room temperature during this time. It is then treated with 400 cc. of approximately 2*N* sulfuric acid, the layers are separated, the aqueous solution is extracted once with ether, and the organic layers are combined. They are washed once with 2*N* sulfuric acid, and then with concentrated bicarbonate solution until no further benzoic acid is obtained on acidification of the bicarbonate extracts. If the benzoic acid is not all removed at this stage, it is troublesome during the distillation. The organic layer is washed with water, dried, the solvent is removed, and the residue distilled through a column. The yield of material of b.p. 144–149° (0.8 mm.) is 35.8–39.4 g. (68–75%), n_{D}^{20} 1.5097. It gives a red color with ferric chloride and its infrared spectrum shows bands, among others, at 1739, 1684, and 1600 cm.$^{-1}$ It gives an ethylamine salt, m.p. 90–92°, as reported,[26] and the copper derivative melts[27] at 182°; treatment with phenylhydrazine in glacial acetic acid gives β-benzoylphenylhydrazine,[10,13] m.p. 169–170°, undepressed when mixed with an authentic sample.[28]

Diethyl benzoylethylmalonate (VII). The magnesium ethoxy enolate was prepared as described above from 37.6 g. of diethyl ethylmalonate. The mixed anhydride was prepared as above from 26.8 g. of benzoic acid, 20.2 g. of triethylamine, and 27.2 g. of isobutyl chlorocarbonate in 400 cc. of toluene. The enolate was added to the mixed anhydride over a 30-min. period at 0°; the mixture was allowed to come to room temperature, was stirred for 2 hr. and was then heated at 50° for 30 min. The mixture was worked up as described above; acidification of the bicarbonate washes yielded 10 g. of benzoic acid. The product was distilled twice, the first distillation yielding a large forerun, and a fraction of 3.49 g., b.p. 125–130° (0.3 mm.), n_{D}^{20} 1.5020.

Anal. (on a redistilled sample, b.p. 126–127° (0.3 mm.), n_{D}^{20} 1.5021). Calcd. for $C_{16}H_{20}O_5$: C, 65.74; H, 6.90. Found: C, 65.40; H, 6.84.

The forerun was distilled through a spinning band column, and an additional fraction of 6.47 g., b.p. 102–108° (0.05 mm.), n_{D}^{20} 1.4997. The combined yield, 9.96 g. is 17%. The compound deposited benzoic acid after standing for several months, and was cleaved by phenylhydrazine to form benzoylphenylhydrazine. The infrared spectrum in the double bond region showed bands at 1724, 1684, 1592, and 1575 cm.$^{-1}$

Diethyl acetylmalonate (VI). This was prepared by the procedure described for diethyl benzoylmalonate. The reaction was run on a 0.2 mole scale, and yielded 12.1 g. of product, b.p. 110–115° (13 mm.), n_{D}^{20} 1.4464 and 5.72 g., b.p. 115–117° (13 mm.), n_{D}^{20} 1.4477.

The forerun was redistilled and yielded 3.78 g., b.p. 108–111° (12 mm.), n_{D}^{20} 1.4471. The combined yield, 21.63 g. was 53.5%. The dinitrophenylhydrazone melted at 146–148°; Lund[8] reported 147°.

3-CARBETHOXY-4-HYDROXYCOUMARIN (IX)

A. By acylation of malonic ester with the mixed anhydride from acetylsalicylic acid. The mixed anhydride was prepared from 39.6 g. (0.22 mole) of acetylsalicylic acid, 20.2 g. (0.2 mole) of triethylamine, and 21.7 g. (0.2 mole) of ethyl chlorocarbonate in 250 cc. of dry toluene, as described above for I. To this anhydride was added the magnesium ethoxy enolate in ether prepared as above from 0.2 mole of malonic ester. The temperature was kept at 0° during the addition, which required about 45 min. The reaction mixture was then allowed to come to room temperature by standing overnight, was treated with 400 cc. of cold 5% sulfuric acid, the organic layer was separated, the aqueous layer was extracted with two portions of ether, and the extracts were added to the organic layer. The combined organic solutions were washed with dilute sulfuric acid, with water, and three times with saturated sodium bicarbonate solution. The solution was dried, and the solvent was removed at atmospheric pressure, and finally *in vacuo*.

The yellow residual oil (40 g.) was stirred with 10% sodium hydroxide at room temperature until the white sodium salt of IX had precipitated completely and the oil had disappeared. The salt was collected by filtration, and acidification of the filtrate yielded 1 g. of impure 3-carbethoxy-4-hydroxycoumarin (IX). The sodium salt was dissolved in hot water, cooled slightly, and acidified carefully with dilute sulfuric acid. The precipitated product weighed 24.5 g., was combined with the above 1 g. from the filtrate, and was recrystallized from ethanol; the product (21.1 g., 45%) melted at 99–101°. Anschutz[16] reported 101°. It showed no depression on mixed melting point with an authentic sample of IX prepared as described by Hultquist.[16]

4-Hydroxycoumarin (X).[16] Hydrolysis of 1.28 g. of the 3-carbethoxy-4-hydroxycoumarin prepared by the mixed anhydride procedure by refluxing with 10% aqueous potassium hydroxide for 8 hr. yielded, after acidification and two crystallizations of the product from water, 4-hydroxycoumarin, m.p. 209–210°. The reported[17] melting point is 210°.

The compound was further characterized by condensation with formaldehyde to 3,3′-methylene-bis(4-hydroxycoumarin), melting point after crystallization from cyclohexanone, 279–281°; the reported[17] melting point is 288–289°.

Acylation of malonic ester by the cyclic carbonic anhydride from salicylic acid (XII). The cyclic anhydride XII was prepared by W. H. Davies' procedure,[18] and melted at 112–118° with decomposition; Davies reported 113–121°. The compound yielded *o*-hydroxybenzophenone when treated with benzene and aluminum chloride, as reported.[18]

The magnesium ethoxy malonic ester was prepared from 0.1 mole of reagents as described previously; it was added dropwise to 16.4 g. (0.1 mole) of the cyclic anhydride (XII) in 175 cc. of dry ether. The reaction mixture was surrounded by an ice bath so that the temperature remained at 0° or

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(26) F. E. King, T. J. King, and G. B. Thompson, *J. Chem. Soc.*, 552 (1948).

(27) H. Bernhard, *Ann.*, **282**, 166 (1894), reported 180°.

(28) E. Fischer, *Ann.*, **190**, 125 (1878).

below during this addition. It was stirred for 4 hr. at 0° and then allowed to reach room temperature on overnight standing. The mixture was decomposed with 200 cc. of sulfuric acid (*ca.* 2*N*) and 20 g. of ice. The aqueous layer was separated and washed twice with ether. The ether layers were combined and washed successively with dilute sulfuric acid, water, saturated sodium bicarbonate solution, and finally with water. Acidification of the bicarbonate washes yielded 13.39 g. of impure salicylic acid.

The organic layer was dried, the ether was removed, and the residue was treated with 10% sodium hydroxide as described above. A small amount of salt precipitated. It was filtered off, was dissolved in water, and the aqueous solution was acidified. Less than a gram of material was obtained, m.p. 100–102° after recrystallization from aqueous ethanol. A mixed melting point with an authentic sample of 3-carbethoxy-4-hydroxycoumarin (IX) remained at 101–102°.

Propiophenone from diethyl cadmium and benzoic-carbonic anhydride (I). Diethyl cadmium was prepared in the usual way[19] from ethylmagnesium bromide (from 0.2 mole of ethyl bromide and magnesium) and 19.6 g. (0.11 mole) of cadmium chloride; the ether solution was refluxed on the steam bath for 30 min. to complete the reaction, at which time there was a negative Gilman reaction for Grignard reagent.

The mixed anhydride was prepared as usual from 19.5 g. (0.16 mole) of benzoic acid, 16.2 g. of triethylamine, and 17.4 g. of ethyl chlorocarbonate. The solution was separated from the precipitated triethylamine hydrochloride by sucking it out through a filter stick inserted into the bottom of the flask. (When the hydrochloride was not removed, no propiophenone resulted from the reaction.) The solution was transferred directly into a cold jacketed dropping funnel without exposure to the atmosphere. The hydrochloride was washed with two fresh 30 cc. portions of dry toluene, and the washes were combined with the above solution.

The solution of the anhydride was added to the cadmium compound with stirring, over a period of 1 hr., keeping the temperature below 2°. The mixture was allowed to come to room temperature overnight. The cake which formed was partially broken up by heating at reflux for 2 hr. The mixture was cooled and decomposed with 200 g. of ice and water followed by the addition of 50 cc. of 20% sulfuric acid. The aqueous layer was separated and washed with two 50-cc. portions of ether, the combined ether layers were washed with 20% sulfuric acid, once with water, and three times with 100-cc. portions of 5% bicarbonate solution. The third bicarbonate wash gave no benzoic acid on acidification; the first two yielded 0.95 g. of benzoic acid.

The organic layer was washed once with water, twice with saturated sodium chloride solution, was dried, the solvent was removed, and the residue was distilled. Three fractions were collected in the range 87–103° (17 mm.), n_D^{20} 1.5251, 1.5274, and 1.5263;[29] the combined fractions weighed 13.0 g. (61%). The semicarbazone melted at 173–174°, and gave no depression on mixed melting point with an authentic sample.

Acylation of veratrole by benzoic-carbonic anhydride; 3,4-dimethoxybenzophenone (XIII). The mixed anhydride was prepared from 3.05 g. of benzoic acid, 2.5 g. of triethylamine, and 2.7 g. of ethyl chlorocarbonate in 40 cc. of carbon disulfide at 0°. After stirring for 15 min., 6.9 g. of powdered aluminum chloride was added over a period of 5 min. After stirring for 5 min., a solution of 3.46 g. of veratrole in 10 cc. of carbon disulfide was added over a 15-min. period. The mixture became green, and was allowed to come to room temperature overnight. Ice water was then added to decompose the mixture, the layers were separated, the flask was washed with 25 cc. of chloroform, and the aqueous layer was washed with 25 cc. of chloroform and 25 cc. of ether. The combined organic layers were washed with two 50-cc. portions of 5% bicarbonate; these washes yielded only 0.25 g. of benzoic acid on acidification. The organic layer was dried, and was concentrated to a yellow oil by passing air over it at 50°. The oil slowly crystallized, and from it was obtained after three crystallizations from dilute ethanol 1.02 g. (17%) of 3,4-dimethoxybenzophenone, m.p. 100.5–101.5°, which showed no depression on mixed melting point with an authentic sample.[30]

The mixed anhydride (0.08 mole), prepared in benzene-ethylene chloride, was freed from triethylamine hydrochloride with a filter stick, was added to 0.073 mole of veratrole, and 0.22 mole of stannic chloride was added. The reaction was carried out essentially as above, and yielded 1.92 g. (11%) of recrystallized dimethoxybenzophenone.

Attempted acylation of veratrole with ethyl benzoate, with benzoic acid and with benzoic anhydride, using aluminum chloride and the conditions described above, gave no isolatable amount of the dimethoxybenzophenone. In the benzoic anhydride run, the noncrystalline oil was distilled, and appeared, from its refractive index and infrared spectrum, to be a mixture of veratrole and benzoyl chloride.

Isobutyl diazomethyl ketone. A solution of the mixed isovaleric-carbonic anhydride was prepared in 175 cc. of dry ether from 0.1 mole of reagents. The anhydride solution was separated from the triethylamine hydrochloride by filtration with a filter stick, the hydrochloride was washed with 50 cc. of cold ether which was combined with the other solution; the anhydride solution was added to an ethereal diazomethane solution prepared from 20.6 g. (0.2 mole) of nitrosomethylurea. After standing 1 hr. at 0° the mixture was allowed to reach room temperature overnight. The ether was removed with an aspirator at 40°, and the dark residue yielded upon distillation 7.2 g. of isobutyl diazomethyl ketone,[31] b.p. 80–100° (18 mm.). The material showed a very strong band at 2085 cm.$^{-1}$, which is characteristic of diazoketones.[32]

The yield of diazoketone was not improved by using 4 moles of diazomethane per mole of anhydride, instead of two as above.

Diazoacetophenone was prepared by the above procedure, and was isolated by crystallization; the yield of twice recrystallized material,[33] m.p. 49–50°, was 7%.

4-Phenylphenyl benzoate. 4-Phenylphenol (17.0 g.) in 120 cc. of ether and 30 cc. of chloroform was added at 0° to a solution of the mixed benzoic-carbonic anhydride prepared from 0.1 mole of reagents in 100 cc. of toluene. The mixture was allowed to come to room temperature overnight, was then heated to 40°, and quickly cooled in an ice bath. The mixture was shaken with water, more toluene was added to dissolve the remaining solid, and the organic layer was washed with saturated bicarbonate, which removed no benzoic acid, and then with 5% sodium hydroxide solution, which removed 3.48 g. of 4-phenylphenol, m.p. 164.5–166°. From the organic layer was obtained a solid, which, after crystallization from alcohol, yielded 14.6 g. (53%) of 4-phenylphenyl benzoate, m.p. 149–150.5°; the reported value[34] is 150°.

Benzyl benzoate. This ester was obtained in 47% yield by addition of an equivalent amount of benzyl alcohol to the benzoic-carbonic anhydride.

Isoamyl benzoate was obtained in 25% yield in a similar manner, from a 0.1 mole run, except that there was an excess of 0.05 mole of triethylamine present over the amount

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(29) O. Wallach, *Ann.*, **332**, 317 (1904), reports n_D^{20} 1.5270.

(30) F. Brüggemann, *J. prakt. Chem.*, **53**, 253 (1896), reported a melting point of 99°.

(31) L. Birkofer, *Ber.*, **80**, 88 (1947).

(32) K. B. Wiberg and T. W. Hutton, *J. Am. Chem. Soc.*, **76**, 5367 (1954).

(33) L. Wolff, *Ann.*, **325**, 142 (1902) reported the same melting point.

(34) J. Kaiser, *Ann.*, **257**, 101 (1890).

necessary to neutralize the hydrogen chloride formed in the mixed anhydride preparation.

2,4-Dimethylpentanol-3 (XIV). 2,4-Dimethylpentanone-3 (86.6 g., b.p. 122–124°, n_D^{25} 1.3981) was added over a period of 1 hr. to a suspension of 8.36 g. of lithium aluminum hydride in 300 cc. of dry ether. The mixture was then refluxed 1 hr., water was added cautiously dropwise until gas evolution ceased, and the reaction mixture was poured into 150 cc. of ice water, to which was added 600 cc. of 10% sulfuric acid solution. The aqueous solution was extracted twice with ether, the ether was washed with water until neutral, was dried, and the solvent was removed. Distillation yielded 66.0 g. (75%) of product,[35] b.p. 133–137°, n_D^{20} 1.4235. The phenylurethan melted at 92.5–94.5°; Conant and Blatt[23] reported 95°.

2,4-Dimethylpentanol-3 chlorocarbonate (XV). In a 250 cc. three-necked flask cooled in a dry ice–acetone bath was condensed 93.0 g. (0.95 mole) of phosgene. The flask was transferred to an ice bath, fitted with a stirrer, a condenser with an outlet tube leading to a drain, and a dropping funnel. The alcohol XIV (76 g., 0.66 mole) was added over a period of 45 min. The ice bath was removed and the mixture was allowed to stand at room temperature overnight. The excess phosgene was removed by an aspirator over a period of 90 min. Distillation at 60–70 mm. yielded material, b.p. 76–90°, n_D^{20} 1.4218–1.4220, which was a mixture of chlorocarbonate and starting material, because it showed absorption at 3330 and 1773 cm.$^{-1}$ Further distillation yielded two fractions, b.p. 90–100°, n_D^{20} 1.4225, and b.p. 99° (n_D^{20} 1.4235). These two fractions weighed 40 g., which is a 34% yield of chlorocarbonate; they showed no absorption at 3330 cm.$^{-1}$; but did have the band at 1773 cm.$^{-1}$

Anal. (sample with n_D^{20} 1.4235). Calcd. for $C_8H_{15}ClO_2$: C, 53.77; H, 8.48. Found: C, 53.62; H, 8.39.

2,4-Dimethylpentanol-3 carbamate (XVI). The chlorocarbonate (1.0 g., n_D^{20} 1.4225) dissolved in 10 cc. of ether at 5° was treated with 15 cc. of concentrated aqueous ammonia; the ether layer was decanted, and the aqueous layer was extracted twice with ether. The white residue obtained from the combined ether layers gave, after two crystallizations from benzene, material of m.p. 124–124.8°. The melting point was raised to 125.2–126.2° by vacuum sublimation.

Anal. Calcd. for $C_8H_{17}NO_2$: C, 60.34; H, 10.76; N, 8.80. Found: C, 60.59; H, 11.00; N, 8.76.

Action of benzoic-2,4-dimethylpentanol-3 carbonic anhydride on ethanol. A solution of the benzoic-carbonic anhydride was prepared in 50 cc. of toluene from 0.05 mole of benzoic acid, triethylamine, and 2,4-dimethylpentanol-3 chlorocarbonate. After this mixture had been stirred at 0° for 20 min., 2.3 g. of absolute ethyl alcohol was added. The mixture was allowed to come to room temperature overnight. The triethylamine hydrochloride was filtered off, washed with toluene, and the combined toluene solutions were washed with saturated bicarbonate. No benzoic acid was obtained on acidification. The toluene solution was washed with water, dried, and the solvent was removed. The residue on distillation yielded 1.57 g. (20%) of material, b.p. 97–102° (21 mm.) which was mainly ethyl benzoate. The fractions (6.31 g., 57%), b.p. 145–155° (22 mm.) n_D^{26} 1.4828–1.4872, were shown to be 2,4-dimethylpentanol-3 benzoate[36] by saponification to benzoic acid and 2,4-dimethylpentanol-3, which was identified through the crystalline phenylurethan.

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(35) These agree with the reported values (G. Poletaeff, *Ber.*, 24, 1309 (1891).

(36) G. Vavon, M. Barbier, G. Thiebaut, *Bull. soc. chim. France*, [5] 1, 812 (1934), report the following properties for this ester: b.p. 141–142° (15 mm.); n_D^{19} 1.4916.

[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF IOWA STATE COLLEGE]

Organotin Compounds: Cyclopentadienyl and Related Derivatives

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Triphenyl-1-cyclopentadienyltin, diphenyldi-1-cyclopentadienyltin, phenyltri-1-cyclopentadienyltin, and diphenyldi-1-indenyltin were prepared. Cyclopentadienyl derivatives of tin are unstable in the presence of air and light. Triphenyl-1-cyclopentadienyltin is readily hydrolyzed by water and is cleaved by bromine and by *n*-butyllithium to yield bis-(triphenyltin)oxide, triphenyltin bromide, and tetraphenyltin, respectively. Triphenyl-1-indenyltin and diphenyldi-1-indenyltin were not hydrolyzed under analogous conditions. Addition products were obtained from the Diels-Alder reaction of triphenyl-1-cyclopentadienyltin with maleic anhydride, with diethyl maleate, and with diethyl acetylenedicarboxylate. Triphenyl-2-furyltin did not react with maleic anhydride under corresponding conditions.

Organometallic compounds containing the cyclopentadienyl group have been reported frequently. The recent interest in metallic derivatives of cyclopentadiene, however, has been centered primarily around the preparation and the properties of bis-(cyclopentadienyl)iron (ferrocene)[1–5] and analogous derivatives[6–11]; and the information accumulated in this area has been reviewed.[12] Very little is known about cyclopentadienyl derivatives of the Group IV-B metals. Organotin compounds of this

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(1) Wilkinson, Rosenblum, Whiting, and Woodward, *J. Am. Chem. Soc.*, **74**, 2125 (1952).

(2) Woodward, Rosenblum, and Whiting, *J. Am. Chem. Soc.*, **74**, 3458 (1952).

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(6) Wilkinson, *J. Am. Chem. Soc.*, **74**, 6146 (1952).

(7) Fischer and Jara, *Z. Naturforschung*, **8B**, 217 (1953).

(8) Wilkinson, Pauson, Birmingham, and Cotton, *J. Am. Chem. Soc.*, **75**, 1011 (1953).

(9) Wilkinson, Pauson, and Cotton, *J. Am. Chem. Soc.*, **76**, 1970 (1954).

(10) Summers, *J. Am. Chem. Soc.*, **76**, 2278 (1954).

(11) Wilkinson, *J. Am. Chem. Soc.*, **76**, 209 (1954).

(12) Fischer, *Angew. Chem.*, **67**, 475 (1955); see also Cotton, *Chem. Revs.*, **55**, 551 (1955).