4.5 g. (0.03 mole) of 1,3-dicyclopropyl-2-butene-1-one in 150 ml. of water was oxidized at room temperature by adding 8.4 g. (0.06 mole) of potassium permanganate during three hours. Excess permanganate was removed with sodium bisulfite, manganese dioxide was separated, and the alkaline filtrate was acidified and continuously extracted with ether for two days. Cyclopropanecarboxylic acid, 0.5 g., was separated from the ether solution by extraction with alkali; the residual ether solution on evaporation gave 2.0 g. of cyclopropyl methyl ketone. A 4.5 g. (0.03 mole) portion of the unsaturated ketone mixed with 16 g. of potassium iodide and 250 ml. of 5% sodium hypochlorite gave, after sixteen hours, 8.0 g. of iodoform. The alkaline filtrate was acidified and extracted with ether, and after separation from iodine, 1.5 g. of cyclopropanecarboxylic acid, b.p. 175–185°, was obtained.

A sample of 1,3-dicyclopropyl-2-buten-1-one, b.p. 104° at 12 mm., $n^{20}D$ 1.4872, d_4^{20} 1.001, was used for infrared absorption measurements and for preparation of the semicarbazone which, when recrystallized from dilute alcohol, melted 142.9–143.4°.

Anal. Calcd. for $C_{11}H_{17}ON_3$: N, 20.27. Found: N, 19.45.

A pure sample of methylcyclopropyl-*t*-butylcarbinol, b.p. 85° at 45 mm., $n^{20}D$ 1.4495, d_4^{20} 0.886, was used for the determination of the infrared spectrum. The MR_D found was 43.09; that calculated from atomic refractivities including the exaltation of 0.6 was 43.69.

Anal. Calcd. for $C_9H_{18}O$: C, 76.0; H, 12.76. Found: C, 75.5, 75.5; H, 12.48, 12.52.

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Difluoromethyl Phenyl Ether

BY REGINALD F. CLARK AND J. H. SIMONS

RECEIVED AUGUST 29, 1955

Ethyl difluoromethyl ether has been made and is reported to be unstable.[1,2]

We wish to report the preparation of difluoromethyl phenyl ether by the reaction of potassium phenoxide with dibromodifluoromethane in anhydrous acetone. It has been found to be stable.

Difluoromethyl phenyl ether is a colorless liquid with a very pungent odor, soluble in ethyl ether, ethyl alcohol, benzene and insoluble in water. In the presence of sulfuric acid, the difluoromethyl phenyl ether decomposes to tars and liberates hydrogen fluoride. Upon refluxing the difluoromethyl phenyl ether with ethyl ether and sodium, the ether splits to form sodium phenoxide and sodium fluoride.

Experimental

Starting Materials.—Dibromodifluoromethane was obtained from the Dow Chemical Co. and fractionated. The potassium phenoxide was prepared from phenol and potassium hydroxide.

Preparation.—Dibromodifluoromethane, 118 g. (0.56 mole), was bubbled through a mixture of 400 ml. of anhydrous acetone and 74 g. (0.56 mole) of potassium phenoxide with stirring, at a rate to keep the temperature below 50°. After the addition of the dibromodifluoromethane was started, the solution turned red and finally dark brown.

After completion of the reaction, the Dewar-type condenser was removed and a mixture of acetone and excess dibromodifluoromethane was distilled from the solution. After removal of 300 ml. of acetone, an equal volume of water was added and the mixture was steam distilled. The difluoromethyl phenyl ether layer was separated from the aqueous layer, dried over anhydrous magnesium sulfate and fractionated at reduced pressure through a 50-cm. column, 8 mm. i.d. packed with $^1/_{16}$ in. glass helices. The difluoromethyl phenyl ether distilled at 66–67° at 30 mm., 139–140° at 763 mm., d^{25}_4 1.171, $n^{25}D$ 1.4460. The amount of difluoromethyl phenyl ether collected was 13.2 g.

To the excess dibromodifluoromethane and the acetone distilled from the original solution, 2 liters of cold water was added and the dibromodifluoromethane which separated was collected, dried and used for subsequent experiments. The amount of dibromodifluoromethane recovered was 50 g. The yield of difluoromethyl phenyl ether based on the dibromodifluoromethane used was 28.3%.

When phenol and potassium hydroxide were substituted for anhydrous potassium phenoxide, the yield was 16.3%.

Anal.[3] Calcd. for $C_6H_5OCF_2H$: C, 58.33; H, 4.20. Found: C, 58.37; H, 4.48.

The molar refractivity calculated from the density and refractive index is 32.58; the value calculated from the sum of atomic refractivities is 32.35.

Degradation.—To 5 g. of difluoromethyl phenyl ether was added 10 ml. of 50% sulfuric acid. A violet semi-solid mass was formed and hydrogen fluoride liberated. The acidity was neutralized with sodium hydroxide. A residue remained which was removed by filtration and which was not readily identified. The filtrate, however, after acidification and extraction with ethyl ether, yielded 1.1 g. of phenol.

To a flask containing 2 g. of sodium metal in 20 ml. of anhydrous ethyl ether was added 5 g. of difluoromethyl phenyl ether. The mixture was refluxed for 12 hours after which the excess sodium was slowly decomposed by adding ethyl ether saturated with water. After acidifying the mixture with 20% hydrochloric acid, the ether layer was separated, dried and distilled, yielding 2.1 g. of unreacted difluoromethyl phenyl ether and 1.6 g. of phenol. The dilute hydrochloric acid layer contained a large amount of fluoride ion.

The authors wish to acknowledge the sponsorship of the Minnesota Mining and Mfg. Co. for part of the work reported in this paper.

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Ultraviolet Absorption Spectra of Derivatives of 2,3,5- and 2,4,5-Trihydroxyacetophenone[1]

BY D. D. CLARKE AND F. F. NORD

RECEIVED MAY 10, 1955

In the course of structural studies[1a] in our laboratory, it became necessary to synthesize certain trihydroxybenzene derivatives as model compounds for comparison of ultraviolet absorption spectra. The syntheses of some intermediates and the absorption spectra of the acetophenones are reported here.

2,3,5-Trimethoxybenzaldehyde[2] was chosen as the starting material for building up an α-substituted propionic acid side chain from the aldehyde group. This aldehyde I was converted to the nitrile II.[3] The variable yield obtained in the preparation of I made it difficult to prepare a sufficient quantity of this intermediate to carry out the projected steps in the synthesis of the desired side chain.

(1) Condensed from a portion of the dissertation of D.D.C. submitted to the Graduate School of Fordham University in partial fulfillment of the requirements for the Ph.D. degree.

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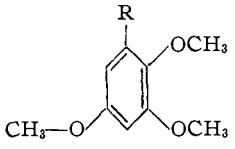
As we were interested in the ultraviolet absorption spectra of derivatives of trihydroxyacetophenone, the aldehyde I was converted to the nitrile III *via* the oxime, and then to the ketone IV.[4] The ultraviolet absorption maximum for this compound is recorded in Table I.

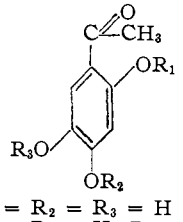
TABLE I

ULTRAVIOLET ABSORPTION MAXIMA OF SUBSTITUTED ACETOPHENONES

Derivative of acetophenone		Wave lengths and intensities of maxima 1st	2nd	3rd
2,4-$(OH)_2$-5-OCH_3	VI	350 (3.86)	276 (4.03)	239 (4.18)
2-OH,4,5-$(OCH_3)_2$	VII	342 (3.89)	275 (4.07)	237 (4.21)
2,4,5-$(OCH_3)_3$	VIII	325 (3.93)	268 (4.02)	232 (4.24)
2,4,5-$(OAc)_3$	IX	342 (2.87)	281 (3.46)	242 (4.02)
2,3,5-$(OCH_3)_3$	IV	313 (3.70)	.....	.....



I, R = CHO
II, R = CH_2CN
III, R = CN
IV, R = $CH_3C(=O)-$



V, $R_1 = R_2 = R_3 = H$
VI, $R_1 = R_2 = H$; $R_3 = CH_3$
VII, $R_1 = H$; $R_2 = R_3 = CH_3$
VIII, $R_1 = R_2 = R_3 = CH_3$
IX, $R_1 = R_2 = R_3 = CH_3C(=O)-$

Other model compounds studied were derivatives of 2,4,5-trihydroxyacetophenone (V) which had absorption maxima at 345 mμ (log ϵ, 3.79) and 280 mμ (log ϵ, 4.00). The spectrum of V was unchanged in the presence of 0.1 *N* hydrochloric acid, but in the presence of 0.1 *N* sodium hydroxide an irreversible transformation took place (Fig. 1). By analogy with the alkaline oxidation of Aureomycin[5] and of di-*t*-butylpyrogallol,[6] it is possible that ring contraction had occurred to give a cyclic β-diketone.

In addition, the ultraviolet absorption spectra of some derivatives of V, *viz.*, VI to IX, were measured and are recorded in Table I.

The ultraviolet absorption spectra of these model compounds showed notable differences from that of the material under consideration and the synthetic studies were not further pursued.

Experimental

2,3,5-Trimethoxybenzaldehyde (I).—Sixty grams of 2,5-dihydroxy-3-methoxybenzaldehyde, prepared as described by Baker, *et al.*,[2] was dissolved in 250 ml. of methanol and heated under reflux. Ten ml. of dimethyl sulfate was added to the reaction mixture followed by 6 ml. of 40% NaOH. When the vigorous reaction had subsided, 5 ml. of dimethyl sulfate was added followed by 6 ml. of alkali. This alternate addition of dimethyl sulfate and base was continued, until a white precipitate of sodium sulfate was formed on the addition of alkali. Three hundred ml. of dimethyl sulfate was required. The reaction mixture was made distinctly alkaline and refluxed for an extra half-hour. After cooling it was extracted with five 200-ml. portions of ether. The ether extract was dried over Drierite and the ether removed under reduced pressure. The yield of crude product varied from 2 to 26 g. and when recrystallized from ligroin (b.p. 90–100°) had a m.p. of 62–63°, literature value 63°.[2]

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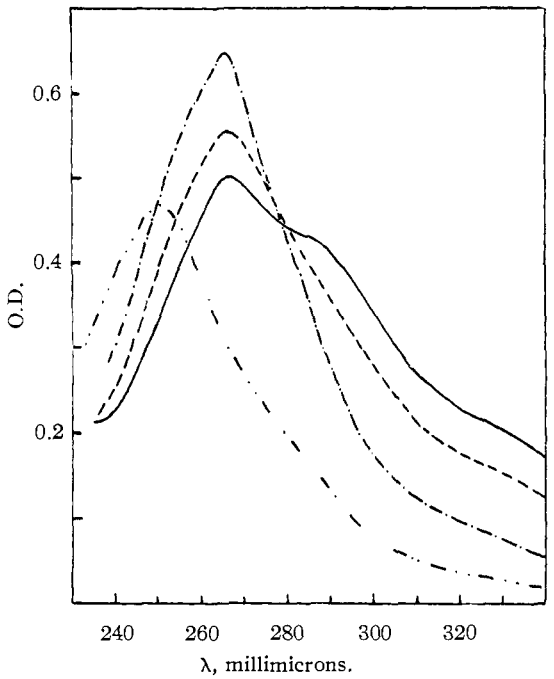

Fig. 1.—Ultraviolet absorption spectrum of 2,4,5-trihydroxyacetophenone in 0.1 *N* NaOH: ——, 0 hr.; – – –, 0.5 hr.; –·–·–, 2.5 hr.; –··–··–··, acidified solution after 5 hr.

The oxime was prepared from 1 g. of the aldehyde in quantitative yield; m.p. 129–130° (recryst. from methanol).

Anal. Calcd. for $C_{10}H_{13}NO_4$: C, 56.86; H, 6.20; N, 6.63; OCH_3, 44.08. Found: C, 56.65; H, 6.11; N, 6.89; OCH_3, 43.89.

2,3,5-Trimethoxybenzylcyanide (II).—Eighteen grams of 2,3,5-trimethoxybenzaldehyde was reduced with lithium aluminum hydride (1 g.) in the usual manner.[7] Ten grams of 2,3,4-trimethoxybenzyl alcohol was obtained after vacuum distillation of the product; b.p. 156–160° at 4 mm.

This alcohol was converted to the corresponding benzyl chloride and then to the cyanide II.[8] The yield was 12 g. After two recrystallizations from petroleum ether the m.p. was 60–63°.

Anal. Calcd. for $C_{11}H_{13}NO_3$: C, 63.75; H, 6.32; N, 6.76; CH_3O, 44.93. Found: C, 63.92; H, 6.84; CH_3O, 44.86.

This compound was also prepared from the aldehyde I by the rhodanine synthesis[8] and found to be identical with the previous product; mixed m.p. 60–62°. The yield by this latter procedure was lower than that obtained by the one described above.

2,4,5-Trihydroxyacetophenone (V).—This compound was prepared by the procedure of Bargellini which consisted in the rearrangement of hydroxyhydroquinone triacetate in the presence of zinc chloride.[9] The trimethyl ether VIII was prepared according to the directions of Mauthner.[10] The 4,5-dimethyl ether VII and the 5-methyl ether VI were prepared as described by Geissman and Seikel.[11] The 5-methyl ether VI was also prepared by treating V with diazomethane in ether solution. For measurement of the ultraviolet absorption spectrum, the crude compound V obtained above was reduced by heating with sodium bisulfite in water solution followed by recrystallization from hot water. This treatment decreased the intensity of the color of the crystals from red to salmon pink and eliminated an absorption peak at 520 mμ.

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2,3,5-Trimethoxybenzonitrile (III).—This compound was obtained from 3 g. of the corresponding oxime by dehydration with acetic anhydride[4]; b.p. 132° (0.2 mm.), m.p. 66–67°.

Anal. Calcd. for $C_{10}H_{11}NO_3$: C, 62.16; H, 5.74; N, 7.25; CH_3O, 48.19. Found: C, 62.35; H, 5.49; N, 7.35; CH_3O, 48.24.

2,3,5-Trimethoxyacetophenone (IV).—One gram of the above nitrile III was treated with methylmagnesium iodide as described by Baker, *et al.*[4] After recrystallization from petroleum ether the m.p. was 60–62°. Mauthner described a product of m.p. 101–102° which he considered to be IV.[10] However, his product was probably VIII which has a m.p. 101–102°.[9]

Anal. Calcd. for $C_{11}H_{14}O_4$: C, 62.84; H, 6.71; CH_3O, 44.29. Found: C, 62.68; H, 6.78; CH_3O, 44.36.

Acknowledgments.—This study was aided by grants from the Research Corporation, the Office of Naval Research, U. S. Public Health Service and the National Science Foundation.

CONTRIBUTION NO. 309 FROM THE DEPARTMENT
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Some Dialysis Experiments with Polypeptides

BY L. C. CRAIG AND T. P. KING

RECEIVED JULY 11, 1955

In the last few years considerable progress has been made in determining the amino acid sequence in polypeptides and a few proteins. The approach has involved partial hydrolysis followed by isolation of a sufficient number of interlocking peptides and determination of their structure so that a unique over-all sequence is revealed. At best it is a laborious procedure requiring much fractionation with ion exchange chromatography, countercurrent distribution, zone electrophoresis and paper chromatography or preferably by all of these techniques since they have different selectivities.

Ion exchange chromatography and zone electrophoresis depend primarily on the differences in charge for their separation while chromatography depends on a combination of properties involving polarity and relative adsorbability. Countercurrent distribution depends on a combination of properties also largely involving polarity or something related to solubility as expressed by the relative preference at equilibrium of a solute for two phases in contact.

It would be of great help in the fractionation of these complex mixtures if even a rough separation could be made solely on the basis of molecular size or weight. The advantages of this with partial hydrolysis are obvious not only from the standpoint of separation but also from the standpoint of attaining higher yields of peptides of a desired size. Milder conditions or shorter hydrolysis times could be used initially and the smaller peptides separated from those of large size. The latter could then be repeated several times with removal of the small peptides after each treatment. With these considerations in mind a number of experiments have been made in the use of partial dialysis.

The rate of escape of solutes through a sintered glass diaphragm has been used for some time[1] for estimating the relative molecular size of molecules. There are many accounts in the literature of the correlation of molecular size with the rate of dialysis through a semi-permeable membrane.[2-4]

Interesting attempts also have been made by Signer, *et al.*,[5] to use the differences in the relative rates of passage through a semi-permeable membrane for the separation of complex mixtures of smaller molecules. In the latter work a train of dialysis cells has been set up so that solution and dialysate flow countercurrently to each other.

A few preliminary experiments have been made in this Laboratory with a series of dialysis units which can give a result strictly on a discontinuous basis in a manner entirely analogous to the approach of countercurrent distribution.[6] The dialysis is performed in such manner that it can be interrupted at each stage when a desired percentage of a given solute has escaped from the solution into the dialysate.

Experimental

The type of dialysis unit chosen for the study is shown in Fig. 1 where A is a cell made from 4.8 cm. glass tubing, 11 cm. in length, supported by a buret clamp. The support B for the dialysis sac is made by cutting a 16 mm. test-tube 60 mm. from the top and fire polishing the lower end. A length of Visking cellophane dialysis tubing #20/32 is then cut and one end closed by tying a knot in the wet casing. The open end is pulled over the glass support B until it reaches the flared upper end of the glass tube. The clamp C closes around the cellophane and the glass tube B and holds both in place. The cellophane sac is cut of such length that 10 cm. of the sac extends below the glass tube B.

D is a glass tube 9 mm. in diameter and approximately 27 cm. in length. It is partially closed on the bottom and serves as a bubble tube for stirring the solution in the dialysis sac. It is supported by the clamp E. A rubber tube connected to its upper end supplies the nitrogen. D is of the size given so that when nitrogen has displaced all the solution from its lower end and with 12 ml. of solution the level of the solution outside D but inside the sac will rise to within 1 cm. of the glass support B. Since the dialysis tubing approximates 5 cm. in circumference approximately 45 sq. cm. of dialyzing surface is afforded.

One hundred-twenty ml. of solvent is placed in the cell A outside the sac. This volume will fill it to a point level with the solution inside the sac. It was found that good stirring resulted from quite slow bubbling of nitrogen through a tube F which extends to the bottom of the cell A. Even with surface active solutes which tended to foam the rate of bubbling could be reduced and effective results still obtained. In this case a drop of octanol was of great help. It was found experimentally that reduction of the rate of bubbling to practically nothing from the tube D inside the sac did not strongly affect the rate of escape of solute through the membrane.

The dialysate could be removed easily by lowering A from the apparatus. The solution could be removed conveniently through the top of D by a polyethylene tube attached to a 20-ml. hypodermic syringe. This disturbed as little as possible the fragile sac so that it could be used repeatedly. A sac was always tested for leakage immediately before use.

Rate studies were made at room temperature with many different solutes. The experiment with phenylalanine will be taken as an example. A sample of 120 mg. of the amino

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