acid. The increase in yield appears to be primarily due to a new method for preparing the anil, I. A solution of *o*-anisidine and ethyl oxaloacetate in ether was refluxed in a Soxhlet extractor using calcium hydride in the extraction thimble, so that the hydride continuously removed the water produced by anil formation. For comparative yields, a preparation of ethyl oxaloacetate (synthesized from ethyl acetate and ethyl oxalate) was divided into two parts, and one part run as originally described[2] (refluxing benzene over $Na_2SO_4$) and one part as described above. Cyclization of the anils without isolation gave yields of 20% and 50%, respectively, of the ester, II, based on ethyl acetate.

It was found that hydrolysis of the ester, II, did not take place effectively, at least on this small scale, using the proportions of potassium iodide and 95% phosphoric acid recommended.[2] However, by increasing the relative amount of phosphoric acid, a nearly quantitative yield of xanthurenic acid was obtained from II.

## EXPERIMENTAL

*Preparation of ethyl oxaloacetate-4-$C^{14}$.* Ethyl acetate-1-$C^{14}$, prepared in approximately 86% yield from 588 mg. (7.17 mM., 4.8 mc.) of sodium acetate-1-$C^{14}$ essentially by the method of Ropp,[3] was mixed with 0.825 ml. of diethyl oxalate in 2 ml. of dry ether. This solution was added dropwise with stirring to a cooled (ice bath) suspension of sodium ethoxide (from 153 mg. of sodium hydride and 0.356 ml. of absolute ethanol) in 2 ml. of dry ether. The mixture was stirred in the cold for 2 hr. and then allowed to stand overnight at room temperature. The resulting grey paste was treated with a solution of 3 ml. of 6N $H_2SO_4$ in 10 ml. of water, and then was extracted 4 times with ether. The combined ether extracts which contained the ethyl oxaloacetate-4-$C^{14}$ were dried over $Na_2SO_4$.

*Formation of the anil* (I). To the ether solution of ethyl oxaloacetate-4-$C^{14}$, still over $Na_2SO_4$, was added 1.2 ml. of freshly distilled *o*-anisidine. A precipitate of *o*-anisidine hydrosulfate was formed, presumably because of a small amount of $H_2SO_4$ carried over from the extraction procedure. The salt was removed by filtration, along with the $Na_2SO_4$. The yellow filtrate was evaporated to a volume of about 20 ml. and transferred to a micro Soxhlet extraction apparatus.[4] The thimble (10 × 50 mm.) was half filled with calcium hydride which had been ground in a mortar, and the apparatus was protected from the atmosphere with a drying tube. After being refluxed for 12 hr. the ether solution was washed with a solution of 1 g. of citric acid in 15 ml. of water in two portions, and then with water. The ether layer was dried ($Na_2SO_4$) and distilled to a small volume. It was then transferred to a 15 ml. pear shaped flask[5] and the last of the ether was removed by gentle distillation, and finally under vacuum. The yellow oil which remained was presumably the anil of *o*-anisidine and ethyl oxaloacetate.

*Ethyl 4-hydroxy-8-methoxy quinaldate-4-$C^{14}$* (II). To the material in the flask was added 3.5 ml. of Dowtherm A, and a small carborundum boiling chip. A reflux condenser was set in place and the flask immersed in an oil bath at 270–280° for 11 min. (Small differences in time apparently do not affect the yield adversely.) The resulting dark brown liquid was cooled and transferred to a separatory funnel with the aid of several ml. of ether. It was extracted 4 times with a total of 6 ml. of 6*N* HCl in 25 ml. of water. The light yellow HCl extracts were washed with ether and the ether layer was discarded. The acid solution was then filtered and carefully made just alkaline with finely powdered sodium carbonate. The resulting mixture was placed in a refrigerator for 3 hr. and the precipitate filtered, washed with water, and dried *in vacuo* over $P_2O_5$. The yield of ester was 0.72 g. or 40.5% based on sodium acetate-1-$C^{14}$.

*Xanthurenic acid-4-$C^{14}$.* The ester was placed in a 20 ml. pear shaped flask, and 11.3 g. of 95% phosphoric acid was added, followed by 7.2 g. of KI. After refluxing in an oil bath at 260° for 1.5 hr. the mixture was cooled and transferred to a 125 ml. Erlenmeyer flask with the aid of 50 ml. of water. The contents of the flask were heated gently and stirred until the black color had disappeared and a bright yellow precipitate remained. The mixture was placed in a refrigerator for several hours, and the yellow solid filtered onto a sintered glass funnel. The product was washed with water and then with alcohol. The crude xanthurenic acid-4-$C^{14}$ was passed through the filter with dilute aqueous NaOH. The filtrate was acidified with dilute HCl and the precipitate collected as above. The process was repeated once again, and the product finally dried *in vacuo* over $P_2O_5$. The yield of xanthurenic acid-4-$C^{14}$ was 0.58 g., or 39% based on sodium acetate-1-$C^{14}$ (97% from the ethyl quinaldate).

*Purity:* Paper chromatographs in two solvents (butanol:acetic acid:water-5:1:4 and methanol:benzene:butanol:water-4:2:2:2) each showed only one spot when examined under ultraviolet light. These spots corresponded exactly to the only spot obtained radioautographically on x-ray film, and the $R_f$ values agreed closely with those reported by other workers. The specific activity of the xanthurenic acid-4-$C^{14}$ was 3.4 $\mu$c/mg. (Calcd.: 3.4 $\mu$c/mg.).

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(3) G. A. Ropp, *J. Am. Chem. Soc.*, **72**, 2299 (1950).
(4) Corning Glass Co., Corning, N. Y.
(5) Metro Industries, Inc., Long Island City, N. Y.

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## New Synthesis of Aryl Esters of Aromatic Acids

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It has been shown by several workers[1–6] that the aluminum chloride catalyzed reaction of alkyl chloroformates with aromatic hydrocarbons behaves in an abnormal manner. Alkylation of the hydrocarbon results instead of formation of the expected alkyl ester of the aromatic acid.

This note describes experiments in which aryl chloroformates react with aromatic hydrocarbons in the presence of aluminum chloride to form the expected aryl esters of aromatic acids.

(1) C. Friedel and J. M. Crafts, *Compt. rend.*, **84**, 1450 (1877).
(2) C. Friedel and J. M. Crafts, *Ann. chim. phys.*, (*6*) **1**, 527 (1884).
(3) E. H. Renne, *J. Chem. Soc.*, **41**, 33 (1882).
(4) F. Kunckell and G. Ulex, *J. prakt. Chem.*, **86**, 518 (1912).
(5) F. Kunckell and G. Ulex, *J. prakt. Chem.*, **87**, 227 (1913).
(6) Buu-Hoï and J. Janicaud, *Bull. soc. chim. France*, **12**, 640 (1945).

EXPERIMENTAL

*Materials.* The aryl chloroformates were synthesized in this laboratory by the method of Raiford and Inman.[7] The aromatic hydrocarbons used were Eastman grade. The aluminum chloride was Baker and Adamson, anhydrous, Reagent grade.

*Phenyl benzoate.* A mixture of 2.0 g. (0.0128 mole) of phenyl chloroformate, 1.75 g. (0.013 mole) of aluminum chloride and 10 cc. of dry benzene was heated on the steam bath under reflux for 1 hr. At the end of this time the evolution of gaseous hydrogen chloride had practically ceased. In all the preparations described it was assumed that the reaction was complete when gas was no longer evolved from the reaction mixture. After cooling to room temperature the reaction mixture was added slowly with stirring to an excess of ice-cooled dilute hydrochloric acid solution. After decomposition of the complex was complete the benzene layer was washed with water and then 5% sodium hydroxide solution. No appreciable precipitate formed when the alkaline extract was acidified. This was an indication that the aryl ester had not undergone the Fries rearrangement to form a hydroxyaryl ketone. The benzene was removed by steam distillation. The nonvolatile oil solidified when the water-oil mixture was cooled in ice, m. p. 66–68°. A mixed melting point of this product with a known sample of phenyl benzoate showed no depression. The yield was 1.62 g. (64%).

*p-Chlorophenyl benzoate.* A mixture of 3.82 g. (0.020 mole) of *p*-chlorophenyl chloroformate, 3.0 g. (0.0225 mole) of aluminum chloride and 20 cc. of dry benzene was refluxed on the steam bath for 5 hr. The reaction product was decomposed with cold dilute hydrochloric acid as previously described. To aid in solubilizing the product in the benzene layer 20 cc. of diethyl ether was added. The benzene-ether layer was extracted with 5% sodium hydroxide solution and then washed with water. After removal of the benzene and ether by steam distillation the nonvolatile oil solidified when the water-oil mixture was cooled to room temperature. The crude product was crystallized from ethyl alcohol using charcoal, m.p. 88–89°. The yield was 2.7 g. (58%). There was no depression of the melting point when the product was mixed with a known sample of *p*-chlorophenyl benzoate which had been prepared by the Schotten-Baumann reaction.

*p-Phenylphenyl benzoate.* A mixture of 11.6 g. (0.05 mole) of *p*-phenylphenyl chloroformate, 8.0 g. (0.06 mole) of aluminum chloride and 30 cc. of dry benzene was heated on the steam bath under reflux for 45 min. The cooled reaction mixture was poured, with stirring, into an excess of cold dilute hydrochloric acid. A rather viscous mass resulted after stirring for 5 hr. After steam was passed through this mixture to remove excess benzene the nonvolatile oily residue solidified when cooled to room temperature. The crude product was crystallized from ethyl alcohol, m.p. 147–148°. A mixed melting point with a known sample of *p*-phenylphenyl benzoate showed no depression. The yield was 7.0 g. (51%).

*Anal.* Calcd. for $C_{19}H_{14}O_2$: C, 83.21; H, 5.11. Found: C, 83.23. 83.10; H, 5.08, 4.96.

*p-Phenylphenyl p-toluate.* A mixture of 11.6 g. (0.050 mole) of *p*-phenylphenylchloroformate, 8.0 g. (0.06 mole) of aluminum chloride and 35 cc. of dry toluene was refluxed for 1 hr. on the steam bath. The cooled reaction mixture was decomposed with dilute hydrochloric acid. After removing the excess toluene by steam distillation it was found that the nonvolatile oil solidified when the water-oil mixture was cooled. This solid was extracted with diethyl ether and the ethereal solution dried with potassium carbonate. The product resulting from the removal of the ether was crystallized from ethyl alcohol, m.p. 131–133°. The yield was 4.2 g. (30%). *p*-Phenylphenol and *p*-toluic acid were identified as the products of hydrolysis of the above substance with alcoholic potassium hydroxide.

(7) L. C. Raiford and G. O. Inman, *J. Am. Chem. Soc.*, 56, 1586 (1934).

*Anal.* Calcd. for $C_{20}H_{16}O_2$: C, 83.33; H, 5.56. Found: C, 83.19, 83.18; H, 5.26, 5.38.

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## Degradation of 3α,17α,21-Trihydroxypregnan-20-one-C$^{14}$ Biosynthesized from Acetate-1-C$^{14}$ by a Cushing's Patient[1,2]

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In a previous communication[3] we reported the distribution of radioactivity in carbons 20 and 21 of cortisol-C$^{14}$ biosynthesized from acetate-1-C$^{14}$ by perfusion of the isolated calf adrenal gland. It was found that carbon 20 was derived from the carboxyl carbon and carbon 21 from the methyl carbon of acetate. This finding agreed with the scheme of Woodward and Bloch[4] for the incorporation of acetate into cholesterol. This communication deals with a similar study on a C$^{14}$-labeled adrenocortical steroid isolated from the urine of a human following the administration of acetate-1-C$^{14}$.[5]

Since there was not sufficient nonlabeled material available to serve as carrier for the degradation, the radioactive steroid, 3α,17α,21-trihydroxypregnan-20-one, was diluted with a related substance with a dihydroxy acetone side chain, 17α,21-dihydroxy-4-pregnene-3,20-dione. The mixture of 3α,17α,21-trihydroxypregnan-20-one-C$^{14}$ and 17α,-21-dihydroxy-4-pregnene-3,20-dione had a corrected specific activity of $80.5 \times 10^3$ counts/min./mM. The mixture was reduced with sodium borohydride and subsequently oxidized with periodic acid to

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(2) Permission was granted by the Atomic Energy Commission to administer 2 mc of acetate-1-C$^{14}$ to a female patient in the terminal stages of adrenal cortical carcinoma. The cooperation of George W. Thorn and staff at the Peter Bent Brigham Hospital, Boston, is gratefully acknowledged.

(3) E. Caspi, G. Rosenfeld, and R. I. Dorfman, *J. Org. Chem.*, 21, 814 (1956).

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