Anal. Calcd. for $C_{18}H_{22}N_4O_4$: C, 55.9; H, 6.8; N, 17.4. Found: C, 55.8; H, 6.8; N, 17.2.

Decarbonmonoxylation of I.—A solution of 8 g. of I ($[\alpha]^{30}D$ −0.18°) and 0.5 g. of *t*-butyl peroxide was refluxed in a 20-cm. Vigreux column fitted with a total condensation, variable take-off head with the heating bath at 180°. Material boiling below 115° was collected. After three additions of 0.1 g. of peroxide over a three-hour period, evolution of carbon monoxide had ceased. The distillate was washed with concentrated sulfuric acid, distilled from sodium and redistilled from potassium to give 2.2 g. of 2,4-dimethylhexane; b.p. 108–110°; $n^{25}D$ 1.3928; d^{25}_4 0.695; $[\alpha]^{22}D$ 0.00 ± 0.01° (reported[4] b.p. 110–111° and d^{21}_4 0.703).[10]

Decarbonmonoxylation of Bicyclo[2.2.2]octane-2-carboxaldehyde (V).—Following Diels and Alder,[6] 128 g. of cyclohexadiene and 180 g. of acrolein was heated 18 hr. at 120° in an autoclave. Distillation yielded 139.3 g. of Δ^5-bicyclo[2.2.2]octene-2-carboxaldehyde, the semicarbazone of which melted 165.5–167° after recrystallization from methanol–water (reported[6] m.p. 176–177°) and could be hydrogenated to the saturated semicarbazone, m.p. 191–192° (reported[6] m.p. 191–192°). Hydrogenation of the unsaturated aldehyde with platinum oxide in glacial acetic acid afforded crude V which was purified through the bisulfite addition product and, somewhat wastefully, by distillation.

Pure V (m.p. 75.5–77°, 6 g.) was refluxed with *t*-butyl peroxide as described above. The product which had sublimed extensively was removed mechanically and sublimed from phosphorus pentoxide and then from sodium to give bicyclo[2.2.2]octane (VI), m.p. 174.5–175°.

Anal. Calcd. for C_8H_{14}: C, 87.2; H, 12.8. Found: 87.0; H, 12.8.

Apocamphane-1-carboxaldehyde (VII).—Following the method of Asahina and Ishidate,[9] a solution of 6 g. of 10-hydroxycamphane, m.p. 199–200°, in 40 cc. of glacial acetic acid was treated with 4 g. of potassium dichromate and shaken for 1 hr. at 80–90°. The reaction mixture was diluted with water and extracted with 5 portions of pentane. The pentane extracts were washed with 3 portions of 10% aqueous sodium carbonate solution and then with saturated sodium chloride, and concentrated to a viscous residue from which 6.6 g. (81%) of VII semicarbazone, m.p. 206–209°, was obtained. Repeated recrystallization from ethanol raised the m.p. to 208–209°, a value considerably below that reported by Asahina and Ishidate,[9] m.p. 220–221°. It is mentionable that the clear melt clouds and decomposes at 210–211°, in part to a solid which melts completely from 245–250°.

Anal. Calcd. for $C_{11}H_{19}N_3O$: C, 63.1; H, 9.2; N, 20.1. Found: C, 63.2; H, 9.3; N, 19.8.

Steam distillation of VII semicarbazone from 7% phosphoric acid followed by extraction with pentane, washing with sodium carbonate, and drying, afforded the aldehyde VII, m.p. 186–188° (reported[9] m.p. 187–189°).

Decarbonmonoxylation of VII.—A mixture of 1.0 g. of VII and 0.8 cc. of *t*-butyl peroxide was heated at 140–150° under reflux in a nitrogen atmosphere, an additional 0.1 cc. of peroxide being added after 1.5 and 2.5 hr., respectively. After 2.75 hr. the vigorous gas evolution having diminished, the temperature was raised to 180° for 10 min. Following distillation of most of the di-*t*-butyl peroxide, the residue was transferred in a little pentane and evaporatively distilled at 100° and 30 mm. The partly solid distillate was dissolved in pentane, washed with aqueous sodium carbonate (from which 5 mg. of apocamphane-1-carboxylic acid was recovered), with aqueous semicarbazide solution, with water, then repeatedly with cold, concentrated sulfuric acid until discoloration ceased, again with water and finally with saturated sodium chloride solution. Careful distillation of the pentane followed by sublimation at 50–60° and 50 mm. yielded 108 mg. of apocamphane (VIII), m.p. 82–87.5° (sealed tube). Resublimation (m.p. 85.5–87.5°), crystallization from methanol, and resublimation from phosphorus pentoxide gave pure material, m.p. 89.5–90.5° (sealed tube).[11] The poor yield is at least in part to be ascribed to the exceptional volatility of the hydrocarbon.

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[10] The physical constants, $n^{25}D$ 1.3925, d^{25}_4 0.694, b.p. 110°, were calculated from the data of A. W. Francis, *Ind. Eng. Chem.*, **33**, 554 (1941).

[11] G. Komppa and T. Hasselström, *Ann.*, **496**, 164 (1932), report m.p. 86° for unrecrystallized VIII.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF CALIFORNIA, LOS ANGELES]

Flavanones and Related Compounds. VII. The Formation of 4,6,3′,4′-Tetrahydroxy-2-benzylcoumaranone-3 by the Sodium Hydrosulfite Reduction of Quercetin

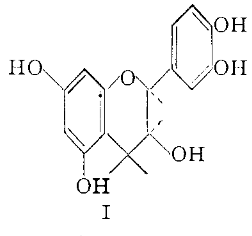
BY T. A. GEISSMAN AND HAROLD LISCHNER

RECEIVED DECEMBER 22, 1951

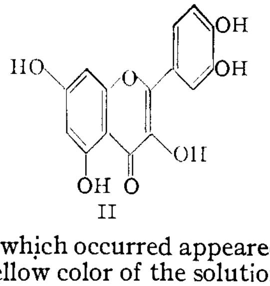
The sodium hydrosulfite reduction of quercetin yields, besides the previously described 2,3-dihydroquercetin, 4,6,3′,4′-tetrahydroxy-2-benzylcoumaranone-3. This was shown to be identical with the compound reported in the literature to have the structure 3,4,3′,4′-pentahydroxy-2-benzylcoumarane.

In the course of experiments aimed at devising a convenient route to the difficultly accessible epicatechin (I) a study has been made of the reduction of certain flavonoid compounds. Since epicatechin has the configuration shown,[1] it was hoped that its synthesis might be accomplished by a reduction of quercetin (II) in which a catalytic reduction of the 2,3-double bond would comprise the step leading to the desired *cis* configuration of the substituents in the 2,3-positions.

It has been reported that quercetin does not absorb hydrogen when platinum oxide is used as the catalyst.[2-4] While our experience did not confirm this, the reduction which occurred appeared to be non-specific. The yellow color of the solution had not disappeared after three moles of hydrogen had been adsorbed, and no homogeneous product was isolated.



I



II

In order to examine the catalytic reduction of dihydroquercetin (III), the latter substance was prepared by the hydrosulfite reduction of quercetin as described by Pew.[4] The flavanonol was formed

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[1] K. Freudenberg and M. Harder, *Ann.*, **451**, 213 (1927); W. Hückel, *ibid.*, **477**, 159 (1929).

[2] K. Freudenberg and A. Kammuller, *ibid.*, **451**, 209 (1927).

[3] R. Mozingo and H. Adkins, THIS JOURNAL, **60**, 669 (1938).

[4] J. C. Pew, *ibid.*, **70**, 3031 (1948).

but accompanying it was a second, previously undescribed, product (IV) which in some runs was isolated in an amount exceeding that of the flavanonol. The new compound had the composition $C_{15}H_{12}O_6$ and gave no color with magnesium and hydrochloric acid; thus, although it was isomeric with eriodictyol, it appeared to be neither a flavone nor a flavanone derivative. Its absorption spectrum (Fig. 1) was typical of those of phloroacetophenone analogs such as 5,7-dihydroxyflavanones. In Fig. 1 is shown for comparison the absorption spectrum of homoeriodictyol (5,7,4′-trihydroxy-3′-methoxyflavanone). Although IV formed a pentaacetate and a pentabenzoate, its R_f value in a paper chromatogram developed with butanol–water–acetic acid[5] was almost identical with that of butein, a tetrahydroxychalcone.

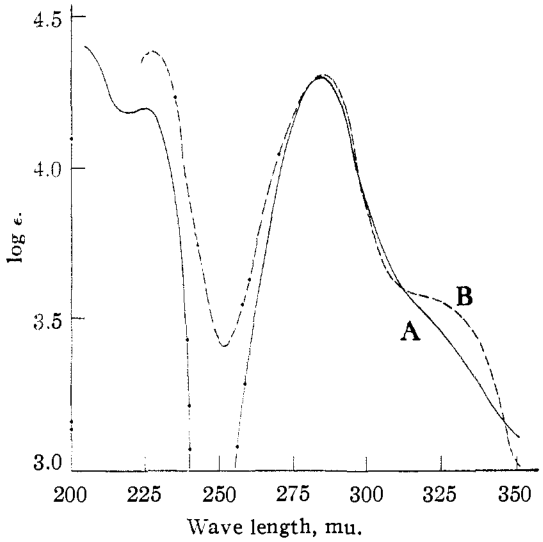
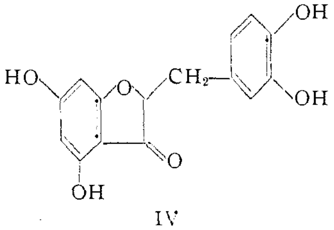
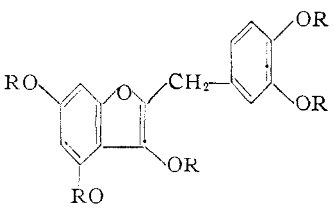


Fig. 1.—Absorption spectra in ethanol: A, 4,6,3′,4′-tetrahydroxy-2-benzylcoumaranone-3; B, homoeriodictyol (5,7,4′-trihydroxy-3′-methoxyflavanone).

These observations led to the conclusion that the new compound was 4,6,3′,4′-tetrahydroxybenzylcoumaranone-3 (IV), and that the pentaacyl derivatives were Va and Vb.



IV



Va, R = CH_3CO-
Vb, R = C_6H_5CO-

In agreement with this conclusion, the absorption spectrum of Va (Fig. 2) showed the intense absorption expected to be associated with the conjugation of the coumarone double bond with the aromatic rings, and the absence of the absorption at 310–330 mμ, shown by IV (Fig. 1), which is to be attributed to the carbonyl group.

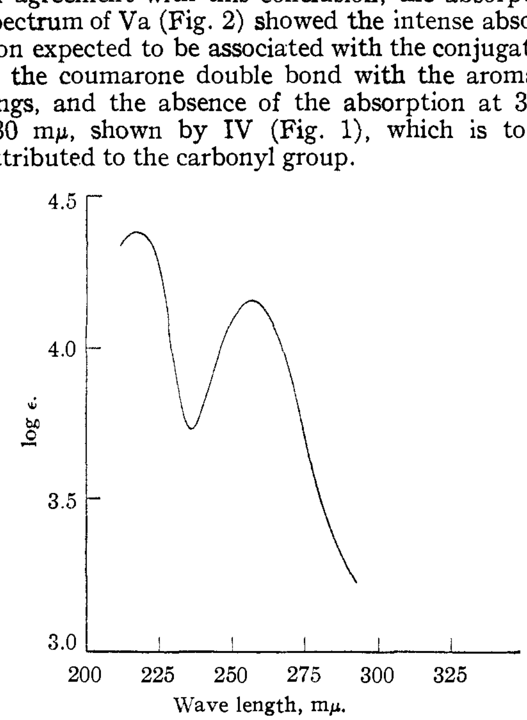
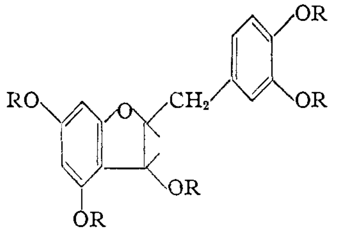


Fig. 2.—Absorption spectrum in ethanol: 3,4,6,3′,4′-pentaacetoxy-2-benzylcoumarone (Va.)

Shriner and Grosser[6] have described the catalytic reduction of 4,6,3′,4′-tetrabenzoyloxybenzalcoumaranone-3 and assigned to the debenzoylated reduction product and its (penta) acetate the structures VI and VII. The melting points reported[6]



VI, R = H
VII, R = CH_3CO-

for the compounds assigned the structures VI and VII were almost identical with those we observed for IV and Va, and made it appear probable that Shriner and Grosser's reduction of the benzalcoumaranone had proceeded only as far as the benzylcoumaranone IV and not to the stage of VI. We had earlier observed that IV was reduced with difficulty and with the slow absorption of hydrogen in amounts corresponding to reduction past the stage of IV. Such behavior during the reduction of tetrabenzoyloxybenzalcoumaranone[6] would have made it appear that more than one mole of hydrogen was absorbed.

A repetition of the experiment of Shriner and Grosser led to the isolation of a product having a melting point (141–142°) corresponding to that reported by these authors (m.p. 138–140°). Hydrolysis of this tetrabenzoate yielded a compound which proved to be identical with the material

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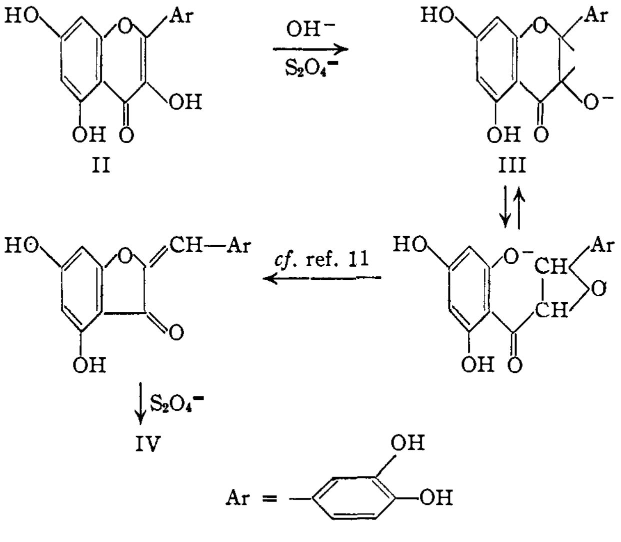
(5) E. C. Bate-Smith, *Biochem. Soc. Symposia*, No. 3 (1948).

(6) R. L. Shriner and F. Grosser, This Journal, **64**, 382 (1942).

(IV) isolated from the hydrosulfite reduction of quercetin. The acetates were identical. The formation of the pentaacyl derivatives Va and Vb from the coumaranone is in accord with much previous experience[7-9]; indeed, it has been found in this Laboratory that it is often difficult to avoid enolacylation of this type.

The formation of IV from quercetin, along with 2,3-dihydroquercetin, clearly involves ring opening at some stage in the process, and an over-all reduction involving two more equivalents of hydrogen than are used in the formation of the flavanonol. The reaction is reminiscent of the formation of flavonols and benzalcoumaranones by the alkaline hydrogen peroxide oxidation of 2'-hydroxychalcones.[10] A likely course for the reduction of quercetin is[11]:



The suggestion that the flavanol is intermediate in the series of changes leading to IV is supported by the observation that the yield of IV increased as the reaction was allowed to proceed for longer periods of time.

Experimental

Hydrogenation of Quercetin.—A solution of 0.3 g. of quercetin in 25 ml. of ethanol was shaken with hydrogen at atmospheric pressure in the presence of 0.1 g. of platinum oxide. One mole of hydrogen was taken up in five hours, 2 moles in 18 hours and 3 moles in 40 hours. The yellow color of the solution had not disappeared by this time. No recognizable reduction products could be isolated.

Reduction of Quercetin with Sodium Hydrosulfite.[4]—The best procedure used in the present work was the following: An intimate mixture of 10 g. of quercetin and 85 g. of sodium carbonate was placed in a 2-l. round-bottom flask equipped with a stirrer and nitrogen inlet and outlet tubes. To the nitrogen-filled flask was added one liter of boiling water, and to the resulting dark-brown solution was added, with stirring and heating with steam, 200 g. of sodium hydrosulfite (74–79% $Na_2S_2O_4$).[12] In five minutes a slow evolution of hydrogen sulfide began; in 12 minutes this had become vigorous. After 25 minutes the flask was cooled in ice and then 130 ml. of concentrated hydrochloric acid was added. After four hours at 0° the mixture was filtered, affording 4.0 g. of recovered quercetin. The filtrate was extracted continuously with ethyl acetate (12 hours), and the ethyl acetyl removed by distillation. The residue crystallized when 100 ml. of water was added, and the resulting suspension was heated to boiling and filtered. The insoluble material (0.9 g.) was the benzylcoumaranone, IV.

The filtrate was treated with norite, filtered, and allowed to cool. The flavanonol (III) which crystallized weighed 3.5 g. and melted at 220–223°. **2,3-Dihydroquercetin (III)**, after repeated recrystallization from water, formed nearly colorless platelets, m.p. 234–235° dec. (reported,[4] 238–241° dec.; 241° dec.[13]). The flavanonol showed the properties (color reactions, formation of multiple hydrates) described by Pew.[4] It formed a **pentaacetate** when treated with acetic anhydride–pyridine (3 hours, 100°). Recrystallized from alcohol, the acetate melted at 149–151°.

Anal. Calcd. for $C_{25}H_{22}O_{12}$: C, 58.36; H, 4.31. Found: C, 58.34; H, 4.29.

The **pentabenzoate** had m.p. 198–200° after recrystallization from ethyl acetate–ethanol.

Anal. Calcd. for $C_{50}H_{32}O_{12}$: C, 72.81; H, 3.91. Found: C, 72.56; H, 3.93.

4,6,3',4'-Tetrahydroxy-2-benzylcoumaranone-3 (IV).—The second product (0.9 g.) isolated as described above was recrystallized from aqueous ethanol until the material gave no color with magnesium–hydrochloric acid. It formed tiny white needles, m.p. 263–264° dec. The material was highly hygroscopic and gave erratic analytical results. A sample (A) recrystallized from ethyl acetate and left in the air for several days, lost 9.85% of its weight on drying *in vacuo* at 100° over phosphorus pentoxide. A second sample (B) recrystallized from water and dried over calcium chloride, lost 8.99% on drying *in vacuo* at 100° ($C_{15}H_{12}O_6 \cdot 1.5H_2O$ contains 8.57% H_2O). The analyses of these samples indicate that they had absorbed water after the final drying, just prior to analysis.

Anal. Calcd. for $C_{15}H_{12}O_6 \cdot 0.5H_2O$: C, 60.60; H, 4.41. Calcd. for $C_{15}H_{12}O_6 \cdot H_2O$: C, 58.82; H, 4.61. Found: (A), C, 60.30; H, 4.62; (B), 58.58; H, 4.80.

3,4,6,3',4'-Tetracetoxy-2-benzylcoumarone (Va).—A solution of 50 mg. of IV in a mixture of 0.5 ml. of acetic anhydride and 0.2 ml. of pyridine was left at room temperature overnight. Water was added and the crystalline precipitate collected and recrystallized from ethanol. The colorless needles melted at 174–175°.

Anal. Calcd. for $C_{25}H_{22}O_{11}$: C, 60.24; H, 4.45. Found: C, 60.05, 60.07, 60.16; H, 4.75, 4.79, 4.30.

3,4,6,3',4'-Tetrabenzoyloxy-2-benzylcoumarone (Vb).—The benzylcoumaranone (IV) was benzoylated with benzoyl chloride in pyridine at room temperature (12 hours). The benzoyl derivative, recrystallized from ethanol, formed colorless needles, m.p. 157–158°.

Anal. Calcd. for $C_{50}H_{32}O_{11}$: C, 74.25; H, 3.99. Found: C, 74.32; H, 4.24.

Reduction of 4,6,3',4'-Tetrabenzoyloxy-2-benzalcoumaranone-3.[7,14]—To a solution of 2.3 g. of 4,6,3',4'-tetrabenzoyloxy-2-benzalcoumaranone-3 in 25 ml. of dioxane was added 100 mg. of platinum oxide and the mixture shaken with hydrogen at an initial pressure of 28 lb. gage. The solution became colorless in about 30 minutes. The reaction was interrupted after two hours and the solution poured into water. The gummy precipitate was taken up in ether and the ether solution dried and concentrated to 30 ml. After the addition of 10 ml. of petroleum ether the solution was kept at 5° until crystallization occurred. The product (1.7 g.) separated in clumps of colorless needles. Recrystallized from dilute acetic acid, the compound formed cottony white needles, m.p. 141–142° (reported,[8] 139–140°).

4,5,3',4'-Tetrahydroxy-2-benzylcoumaranone-3 (IV).—The hydrolysis of the tetrabenzoate was carried out as described by Shriner and Grosser. The product, recrystallized from dilute ethanol, formed tiny white needles, m.p.

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[7] E. Späth, P. Wessely and G. Kubzek, *Ber.*, **70B**, 243 (1937).

[8] R. L. Shriner and M. Witte, THIS JOURNAL, **63**, 2134 (1941).

[9] L. I. Smith, J. A. King, W. I. Guss and L. Nichols, *ibid.*, **65**, 1594 (1943).

[10] T. A. Geissman and D. K. Fukushima, *ibid.*, **70**, 1686 (1948).

[11] It is not possible to specify the exact state of ionization of all of the hydroxyl groups, and those which are shown as ionized are the ones directly involved in the transformations suggested.

[12] D. M. Yost and H. Russel, "Systematic Inorganic Chemistry," Prentice-Hall, Inc., New York, 1944, pp. 354–356.

[13] E. F. Kurth, H. J. Kiefer and J. K. Hubbard, *Timberman*, **49**, 130 (1948); *C. A.*, **42**, 4977 (1948).

[14] A sample of the benzalcoumaranone[4] was kindly furnished by Mr. Eugene Jorgensen.

263–264° dec. A mixed melting point with the quercetin reduction product was 263–264° dec.

The acetyl derivative, prepared by boiling briefly a solution of the tetrahydroxy compound in a mixture of acetic anhydride and pyridine, melted at 174–175°, and did not depress the m.p. of the acetate of the quercetin reduction product.

The absorptioh spectra were determined with a Beckman model DU spectrophotometer.

LOS ANGELES, CALIFORNIA

[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT, UTICA COLLEGE OF SYRACUSE UNIVERSITY]

The Effects of Alkyl Groups Linked to Conjugated Systems. I. The Alkaline Hydrolysis of Some Ethyl *p*-Alkylbenzoates[1]

BY RALPH L. HERBST, JR.,[2] AND MARILYN E. JACOX

The specific reaction rate constants for saponification of a series of ethyl *p*-alkylbenzoates were determined at 30.00 and 60.09° in 87.83% by weight ethanol. The alkyl groups followed the inductive order.

The order of inductive effects of alkyl groups in order of their increasing electron-repulsive character is methyl < ethyl < *i*-propyl < *t*-butyl. When linked directly to an aromatic system, these alkyl groups follow the reverse order for reactions involving electron movement toward the reaction center. This latter series has been explained by hyperconjugative resonance and was first observed by Baker and Nathan[3] in the reaction between *p*-alkylbenzyl bromides and pyridine. Recently, Berliner and Berliner[4] have explained their results on the bromination of alkylbenzenes on the basis of hyperconjugation. Some question of steric hindrance might be raised since the ortho-para ratios have not been determined.[5] According to Berliner and Bondhus,[6] the inductive series can also be explained by resonance; but this introduces a situation difficult to explain—why are two opposing orders based on the same resonance effect operative?

Since only one study[7] at a single temperature has been reported for the effects of alkyl groups on a side chain reaction whose rate is facilitated by the withdrawal of electrons from the reaction center (Ingold and Rothstein's "class B"), it seemed desirable to study carefully the alkaline hydrolysis of a series of ethyl *p*-alkylbenzoates. The mechanism[8] of this reaction is comparatively well understood; the rate-determining step is the nucleophilic attack of a hydroxyl ion at the carbonyl carbon of the ester group. The extensive investigations of Tommila[9] and Kindler[10] have shown that the reaction is favored by *m*- and *p*-electron-attractive substituents, which tend to withdraw electrons from the side chain. Kindler[10] has reported reaction velocity constants of 0.0229, 0.0222 and 0.0230 liter mole^{-1} min.$^{-1}$ for the *p*-methyl-, *p*-ethyl- and *p*-*n*-propyl derivatives for the reaction at 30° in a 87.83% by weight ethanol solvent, whereas Lincoln[11] has found values of 0.00102 and 0.00121 liter mole^{-1} sec.$^{-1}$ for the *t*-butyl and the *p*-methyl compounds, respectively, in a 56% by weight acetone solvent at 25°. It was of interest, therefore, to extend these studies to include more alkyl groups and to determine whether or not the alkyl groups followed the hyperconjugative or inductive order (or some combination of these).

Method.—The saponification rates were determined at 30.00 and 60.09° by the titration method using the 87.83% by weight ethanol solvent employed by Kindler,[10] using cresol red as indicator. A perusal of the literature revealed that the ethyl, *p*-*n*-butyl-, *p*-*s*-butyl-, *p*-*s*-amyl- and the *p*-*t*-amylbenzoates had not been prepared previously. They and the other *p*-alkyl esters in this study were obtained in 55–60% yield by esterification[12] of the corresponding *p*-alkylbenzoic acids with absolute ethanol. The acids were prepared from the appropriate *p*-alkylphenyl methyl ketones by the method of Newman and Holmes.[13]

Experimental

Materials.—Absolute ethanol (Publicker) was employed. Several runs using absolute ethanol which had been distilled over calcium metal gave the same results. Freshly boiled distilled water was used in the preparation of solutions containing water. Carbonate-free sodium hydroxide stock solutions were prepared by dissolving chemically pure sodium hydroxide in water to make a 50% solution. The concentrated solution was allowed to stand in a covered container for 24 hours after which the clear liquid was filtered to remove the sodium carbonate. Stock solutions of 0.02 *N* and 0.5 *N* sodium hydroxide were prepared and their concentration checked with potassium acid phthalate at least every five days. The 0.02 *N* hydrochloric acid solutions were prepared from chemically pure concentrated acid. The m.p.'s of the *p*-alkylbenzoic acids checked with those recorded in the literature. The ethyl *p*-alkylbenzoates were purified by repeated vacuum distillations using a (14 × 1 cm.). Vigreux column: Eastman Kodak Co., ethyl benzoate ($n^{20}\mathrm{D}$ 1.5052; b.p. 101–102° (20 mm.)); *p*-ethyl- ($n^{20}\mathrm{D}$ 1.5011; b.p. 129–130° (15 mm.) (lit.[14] 129–130° (15 mm.)); *p*-methyl- ($n^{20}\mathrm{D}$ 1.5084; b.p. 110–111° (13 mm.) (lit.[14] 110–111° (13 mm.)); *p*-*n*-propyl- ($n^{20}\mathrm{D}$ 1.5003; b.p. 138–139°

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[1] Presented before the Organic Division at the Boston Meeting of the American Chemical Society, April, 1951.

[2] M. W. Kellogg Co., Jersey City, N. J.

[3] J. W. Baker and W. S. Nathan, *J. Chem. Soc.*, 1844 (1935).

[4] For leading references see E. Berliner and F. J. Berliner, THIS JOURNAL, **72**, 222 (1950).

[5] F. A. Matsen, W. W. Robertson and R. L. Chuoke, *Chem. Revs.*, **41**, 279 (1947).

[6] E. J. Berliner and F. J. Bondhus, THIS JOURNAL, **70**, 854 (1948).

[7] J. W. Baker and M. L. Hemming, *J. Chem. Soc.*, 191 (1942).

[8] A. E. Remick, "Electronic Interpretations of Organic Chemistry," John Wiley and Sons, Inc., New York, N. Y., 1943, pp. 395, 400, 405.

[9] E. Tommila, *Ann. Acad. Sci. Fennicae*, Ser. **A57**, No. 13, 3-24 (1941); *C. A.*, **38**, 6172 (1944).

[10] (a) K. Kindler, *Ann.*, **450**, 1 (1926); (b) *ibid.*, **452**, 90 (1927); (c) *ibid.*, **464**, 278 (1928); (d) *Ber.*, **69B**, 2792 (1936).

[11] D. C. Lincoln, Ph.D. Thesis, Notre Dame University, 1949.

[12] L. F. Fieser, "Experiments in Organic Chemistry," 2nd Ed., D. C. Heath and Co., New York, N. Y., p. 62.

[13] M. S. Newman and H. L. Holmes, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 428.

[14] I. Heilbron, "Dictionary of Organic Compounds," Oxford University Press, New York, N. Y., 1946.