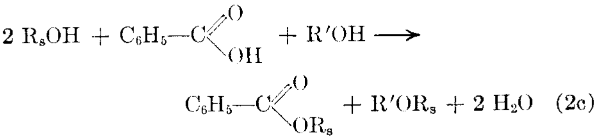
TABLE II

CONVERSION OF ESTRADIOL BENZOATE (13.31×10^{-6} Mole) IN METHANOL-WATER AND ETHANOL-WATER MIXTURES

Alcohol concentration per cent by weight Methanol	Ethanol	*Found in effluent* Methyl benzoate in methanol 10^{-6} Mole	Conversion, %	Ethyl benzoate in ethanol 10^{-6} Mole	Conversion, %
99.96	99.56	13.18	99.0	13.31	100.0
90	90	12.44	93.5	11.26	84.6
80	80	10.63	77.9	9.68	72.7
70	70	8.20	61.6	8.32	62.5
—	60	—	—	7.21	54.9
—	50	—	—	6.50	48.8

It can be noted that the greater the amount of water, the less is the conversion into methyl or ethyl benzoate, *i.e.* the more benzoic acid is formed and retained by the resin. The first step of the reaction between estradiol benzoate and the resin in the hydroxyl form can be represented by the equation (2a), substituting H for R. In this step estradiol benzoate is saponified to estradiol and to benzoic acid (instead of alkyl benzoate). The mechanism of this reaction is the same as in a normal ester hydrolysis.[5] In the second step benzoic acid and estradiol are taken up by the resin:



$$2\,R_sOH + C_6H_5{-}C(=O)OH + R'OH \longrightarrow C_6H_5{-}C(=O)OR_s + R'OR_s + 2\,H_2O \quad (2c)$$

Thus, whether the reaction of an ester (estradiol benzoate) with an anion exchange resin in alcohol-water mixture lies in favor of alcoholysis or hydrolysis, seems to depend primarily upon the equilibrium of the reaction (1). Studies of this equilibrium and its influence upon the ester hydrolysis in anion exchangers are now in progress and will be published in forthcoming papers.

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Some Hydroxyfluorene Derivatives[1]

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3-Hydroxyfluorene has been prepared by two different procedures in the literature. Harradence and Lions[3] have prepared it from 1-indanone in 5 steps. The procedures of Ullmann and Bleier[4] and Lothrop[5] give the compound in 6 steps starting from anthranilic acid. Based on the work of Errera and La Spada[6] a three-step procedure starting from 1,3-indandione has been developed in our laboratory. Using the same procedure 2-acetyl-3-hydroxy-9-fluorenone and 2-ethyl-3-hydroxyfluorene have been prepared. Various other types of 3-hydroxyfluorene derivatives could be made available by this method.

The correct assignment of structure for 3-hydroxyfluorene and 2-ethyl-3-hydroxyfluorene is evident from the close u.v. spectral resemblance of these compounds to 3-methoxyfluorene,[7] Table I. 2-Ethyl-3-hydroxyfluorene and 2- and 3-hydroxyfluorene have an O–H stretching frequency at 2.80 μ in carbon tetrachloride solution. The ethyl derivative has a greatly strengthened aliphatic C—H stretching frequency at 3.4–3.5 μ.

2-Acetylamino-3-hydroxyfluorene has been synthesized in 30% over-all yield from 3-hydroxyfluorene by a procedure that involved chromatography.[8] As it was necessary to prepare a large quantity of the acetylaminohydroxy derivative, a simplified procedure was developed involving coupling of benzenediazonium chloride with 3-hydroxyfluorene, and reduction to the amine hydrochloride followed by acetylation. Starting from 3-hydroxyfluorene the over-all yield was about 68%.

The structure of the 2-acetylamino-3-hydroxyfluorene was based on spectroscopic data and melting point. The ultraviolet-visible absorption spectrum of the phenylazo-3-hydroxyfluorene is entirely different from the spectrum of 2-ethyl-3-hydroxy-4-phenylazofluorene in alcohol, Fig. 1. This and the following data clearly show that the phenylazo group is in the 2-position. The 2-acetylamino-3-hydroxyfluorene obtained from the 2-phenylazo derivative had ultraviolet absorption maxima and minima and molar extinction coefficient values almost identical with that reported by the Weisburgers.[8]

Nitration of 2-acetoxyfluorene gave the 7-nitro derivative. This procedure gave a much purer product than was obtained from 7-nitro-2-aminofluorene,[9] for the 7-nitro-2-hydroxyfluorene derived from the latter compound was found to contain a persistent impurity.

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[1] This investigation was supported by Research Grant C-1066 from the National Cancer Institute, National Institutes of Health, Public Health Service.

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(3) Harradence and Lions, *J. Proc. Roy. Soc. N.S. Wales*, **72**, 284 (1939); *Chem. Abstr.*, **33**, 6825 (1939).

(4) Ullmann and Bleier, *Ber.*, **35**, 4273 (1902).

(5) Lothrop, *J. Am. Chem. Soc.*, **61**, 2115 (1939).

(6) Errera and La Spada, *Gazz. chim. ital.*, **35**, 539 (1905).

(7) Neish, *J. Org. Chem.*, **16**, 694 (1951).

(8) Weisburger and Weisburger, *J. Org. Chem.*, **19**, 964 (1954).

(9) Weisburger and Weisburger, *J. Chem. Soc.*, 758 (1954).

TABLE I

SPECTRAL DATA OF 3-HYDROXYFLUORENE DERIVATIVES[a]

Compound	λ_{max} (log ϵ)		
3-Methoxyfluorene[b]		260 (4.25) 270 (4.22)	307 (4.1) 313 (4.1)
3-Hydroxyfluorene	234 (4.04)	260 (4.14) 268 (4.10)	306 (3.94) 312 (3.95)
2-Ethyl-3-hydroxyfluorene	234 (4.10)	264 (4.19) 272 (4.19)	*310*[c] (4.07) 315 (4.10)
2-Acetyl-3-hydroxy-9-fluorenone	242 (4.14) 287 (4.66)	346 (3.71) 360 (3.68)	~460 (2.05)
2-Carboxy-3-hydroxy-9-fluorenone	260 (4.59) 284 (4.50)	334 (3.60) 350 (3.56)	~*450* (2.05)
2-Phenylazo-3-hydroxyfluorene	*230* (4.18)	*270* (3.91) 278 (3.96)	368–380 (4.39) 400–402 (4.40) *425* (4.28)
4-Phenylazo-3-hydroxy-2-ethylfluorene	*231* (4.28) *237* (4.25)	264 (4.38)	368–375 (4.35) *450* (3.75)

[a] In 95% ethanol. [b] In chloroform.[6] [c] Italicized values are shoulders.

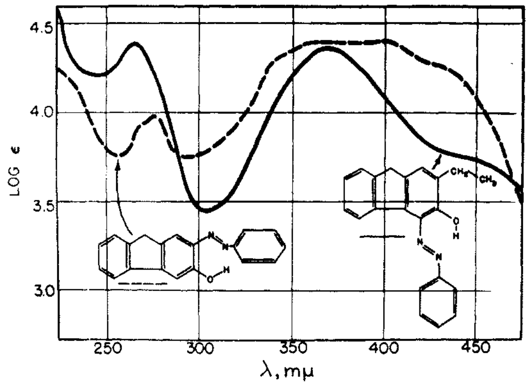

FIG. 1.—THE ABSORPTION SPECTRA OF 2-PHENYLAZO-3-HYDROXYFLUORENE (– – – –) AND 2-ETHYL-3-HYDROXY-4-PHENYLAZOFLUORENE (————) IN 95% ETHANOL.

EXPERIMENTAL[10]

3-Hydroxyfluorene. A solution of 2.4 g. of 2-carboxy-3-hydroxy-9-fluorenone,[6] 1.6 ml. of 85% hydrazine hydrate solution, and 1.6 g. of sodium hydroxide in 24 ml. of ethylene glycol was refluxed for 3 hours. The condenser was removed and the solution was evaporated until the boiling point reached 205°. The solution then was refluxed for 2$^1/_2$ hours, cooled, and poured into a mixture of ice and hydrochloric acid. Filtration gave 1.7 g. (93%) of a white product, m.p. 132–134°. Crystallization from hexane gave 1.6 g. (88%) of colorless plates, m.p. 137–138°. Lit. m.p. 136–137°.[5]

2-Phenylazo-3-hydroxyfluorene. To 0.93 g. of aniline was added a mixture of 8 g. of ice and 4 ml. of concentrated hydrochloric acid. An aqueous solution of 0.76 g. of sodium nitrite was added to the ice-cold stirred mixture. This cold solution then was added dropwise to a stirred solution of 1.82 g. of 3-fluorenol in 22 ml. of 15% aqueous potassium hydroxide and 30 g. of ice. The mixture was stirred an additional hour and filtered to give a quantitative yield of crude product, m.p. 155–159°. Crystallization from hexane gave 2.18 g. (76%) of gold-orange needles, m.p. 170–170.5°.

Anal. Calc'd for $C_{19}H_{14}N_2O$: N, 9.8. Found: N, 10.2.

2-Amino-3-hydroxyfluorene hydrochloride. A solution of 2 g. of stannous chloride hydrate in 15 ml. of concentrated hydrochloric acid was added gradually to a boiling solution of 1 g. of 2-phenylazo-3-hydroxyfluorene in approximately 250 ml. of alcohol. The mixture was allowed to cool, evaporated to $^1/_3$ volume, and enough concentrated hydrochloric acid was added to bring the volume to about 130 ml. The solution was allowed to cool. A practically quantitative yield of beautiful, long, colorless needles of the hydrochloride was obtained. The compound can be crystallized from hydrochloric acid but was characterized through the N-acetyl derivative.

2-Acetylamino-3-hydroxyfluorene. This compound was prepared in almost quantitative yield by the procedure of Weisburger and Weisburger.[8] The compound melted at 237–238° after crystallization from dilute acetic acid. Lit. m.p. 238°.[8] With alcoholic ferric chloride this compound gave a dark green color.

2-Acetyl-3-hydroxy-9-fluorenone. A solution of 2.9 g. of 1,3-indandione and 4.3 g. of sodium carbonate in 30 ml. of water was added slowly with stirring to 10 ml. of 3-ethoxymethyleneacetylacetone[11] at 0–5°. This mixture was refluxed with a solution of 30 ml. of 50% potassium hydroxide for 20 minutes. The precipitate of bis-2,2'-(1,3-indandione)methylidyne was collected. Crystallization from xylene gave 0.9 g. (30%) of red needles, m.p. 316–316.5°. Lit. m.p. 311–313°.[6] Excess cold dilute hydrochloric acid was added to the filtrate and the precipitate was crystallized from Methyl Cellosolve[12] to give 2.0 g. (42% yield based on indandione) of orange plates of the fluorenone derivative, m.p. 234–235°. In one experiment starting from 113 g. of 3-ethoxymethyleneacetylacetone and 40 g. of 1,3-indandione, 12.8 g. (31%) of bis-2,2'-(1,3-indandione)-methylidyne, m.p. 316–316.5° (xylene), and 30 g. (46%) of 2-acetyl-3-hydroxyfluorenone, m.p. 234–235°, were obtained.

Anal. Calc'd for $C_{15}H_{10}O_3$: C, 75.6; H, 4.37. Found: C, 76.0; H, 4.24.

2-Ethyl-3-hydroxyfluorene. The reduction procedure for 2-acetyl-3-hydroxy-9-fluorenone was similar to that used for the 2-carboxy analog, except that twice as much hydrazine hydrate was necessary. An 80–90% yield of colorless plates, m.p. 147.5–148.5°, was obtained after crystallization from heptane.

Anal. Calc'd for $C_{15}H_{14}O$: C, 85.7; H, 6.67. Found: C, 86.0; H, 6.88.

4-Phenylazo-2-ethyl-3-hydroxyfluorene. By the procedure used for the previous azo dye, diazotized aniline was combined with 2-ethyl-3-hydroxyfluorene dissolved in a mixture of aqueous potassium hydroxide and dimethylformamide. Crystallization from hexane (twice) and alcohol (twice) gave

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(10) Melting points are uncorrected. Analyses are by Peninsular ChemResearch, Inc., Gainesville, Florida.

(11) Claisen, *Ber.*, **26**, 2731 (1893).

(12) Trade name (Carbide and Carbon Chemicals Corp.) for 2-methoxyethanol.

an approximately 50% yield of dark red, cottony needles, m.p. 191–192°.

Anal. Calc'd for $C_{21}H_{18}N_2O$: C, 80.3; H, 5.73; N, 8.92. Found: C, 80.4; H, 5.68; N, 8.80.

2-Nitro-7-acetoxyfluorene. (*a*). A mixture of 0.45 ml. of nitric acid (*d.* 1.42) and 1 ml. of acetic anhydride was added to 0.45 g. of 2-acetoxyfluorene[13] at 60°. The solution was warmed to 80° and held at that temperature for 5 minutes. The solid was separated and washed with acetic acid, water, and then with methanol. It melted at 191–192°. Crystallization from alcohol gave about 0.4 g. (75%) of lustrous, yellow, thread-like needles, m.p. 194–195°.

(*b*). Excess acetic anhydride and 1.14 g. of 7-hydroxy-2-nitrofluorene, m.p. 248–250°, were vigorously refluxed for 1 hour. The mixture was poured into water. Two crystallizations from kerosene and two from alcohol gave feathery yellow crystals, m.p. 191–192°. The mixture melting point with product (*a*) was 191–195°. The infrared spectra of (*a*) and (*b*) in chloroform were identical.

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[13] Claborn and Haller, *J. Am. Chem. Soc.*, 59, 1055 (1937).

A Novel Condensation of Benzonitrile Catalyzed by Mercuric Acetate

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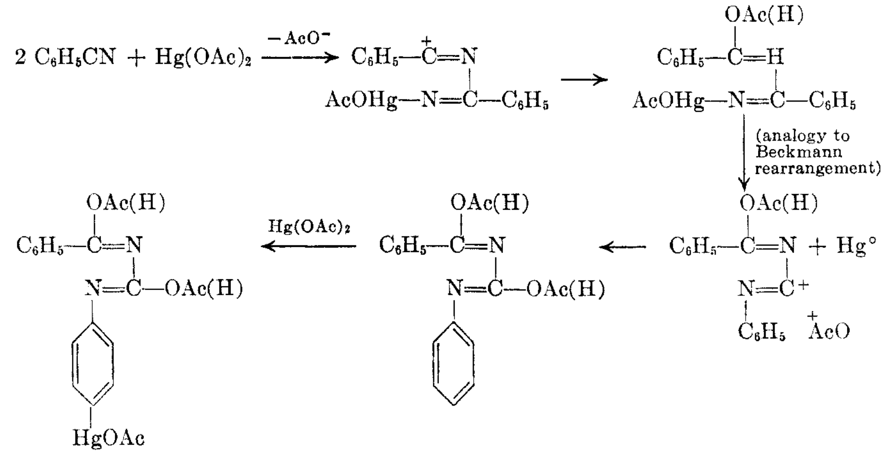
In the course of our investigation on a peculiar orientation in the mercuration of various aromatic compounds in acetic acid,[1] it was noted that no mercuration occurred on the benzene nucleus of benzonitrile. However, the mercurating agent attacked the cyano group, giving a phenyl-rearranged condensate which contained mercury and which on bromination gave N-benzoyl-N′-(*p*-bromophenyl)urea.

It is of interest to note that this reaction involves a rearrangement of a phenyl group. A plausible course for this rearrangement is assumed tentatively to be that shown in the diag;om below. The amount of mercury liberated is in agreement with the above stoichiometry. If a sufficient amount of mercuric acetate is used, mercurous acetate is produced instead of mercury.



EXPERIMENTAL

N-Benzoyl-N′-(p-bromophenyl)urea. In a flask provided with a ground glass reflux condenser, there was placed a solution of freshly distilled benzonitrile (7 g.) and commercial mercuric acetate (10 g.) in glacial acetic acid (50 ml.). This was boiled for 7 hours. Deposition of metallic mercury (2.1 g.) was recognized in the reaction mixture. The cooled mixture was poured into a concentrated aqueous solution (200 ml.) of sodium chloride; a small amount of unreacted benzonitrile (*ca.* 2.5 g.) was removed by extraction with ether. An aqueous solution of sodium hydroxide was added with ice-cooling to the clear salt solution until the solution became slightly alkaline. The resulting voluminous white precipitate of the mercuric compound was filtered. The product, suspended in an aqueous solution of potassium bromide, was treated dropwise with bromine. After the gradual disappearance of the solid material, a new precipitate appeared. The precipitate, after recrystallization from aqueous methanol, gave white crystals (m.p. 233°); the yield was 3.8 g. (27%). No melting point depression was observed on admixture with an authentic sample of N-benzoyl-N′-(*p*-bromophenyl)urea prepared by the benzoylation of N-(*p*-bromophenyl)urea.[2]

The yield was somewhat improved to *ca.* 32% by the use of an increased amount of mercuric acetate (1.5 moles per mole of benzonitrile). On addition of aqueous sodium chloride to this reaction mixture, there was obtained a certain amount of a precipitate of mercurous chloride.

Hydrolysis of the mercuration product. Another crop of the mercuric compound was hydrolyzed with 6 *N* sodium hydroxide to yield benzoic acid (m.p. and mixture m.p. 121°), aniline (m.p. of acetanilide and mixture m.p. 115°), and mercuric oxide.

Other related condensations. The reaction did not occur with benzamide or with an equimolar mixture of benzamide and benzonitrile in the presence of a mercuric salt. The same reaction was attempted with the addition of a small amount of acetic anhydride or water, but the condensation was not recognized in either experiment; *i.e.*, the solution containing

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[1] Ogata and Tsuchida, *J. Org. Chem.*, 20, 1637, 1643 (1955).

[2] Moore and Cederholm, *J. Am. Chem. Soc.*, 28, 1191 (1906).