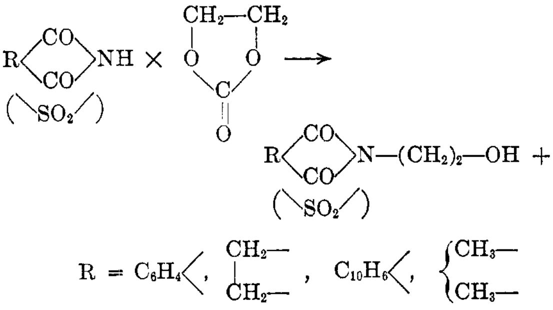
TABLE I

HYDROXYETHYLATION OF IMIDES

Imide	E.C.[a] (mol.) / Imide (mol.)	Alkali	Temp.	Time, Hr.	Yield, %
Phthalimide[b]	1.1	. . .	200	1.0	95
K-phthalimide[c]	2–3	. . .	140–160	0.5	60
Naphthalimide[d]	2.0	. . .	210	1.0	96
Succinimide[e]	1.0	Na_2CO_3 (0.5%)	190	1.0	86
Diacetamide[f]	1.0	Na_2CO_3 (0.5%)	195	1.0	70
Saccharin[g]	1.0	NaOH (0.5%)	210–220	1.0	93

[a] "E.C." represents ethylene carbonate. Product of American Cyanamid Co. [b] *Org. Syntheses*, **Coll. Vol. I**, 457 (1948). [c] *Org. Syntheses*, **Coll. Vol. I**, 119 (1948). [d] T. Maki and H. Hashimoto, *J. Chem. Soc. Japan*, (*Ind. Chem. Sec.*), **54**, 480 (1951). [e] *Org. Syntheses*, **Coll. Vol. II**, 562 (1943). [f] L. Vanino, *Handbuch der Preparativen Chemie* (*2 Auflage*), Ferdinand Enke, Stuttgart, II Bd., p. 207. [g] This was precipitated from the aqueous solution of its sodium salt by dilute hydrochloric acid, m.p. 225–227°.

out alkali carbonate or hydroxide. Aliphatic dicarboxylic imides reacted in the presence of alkali carbonate. Saccharin reacted only in the presence with alkali hydroxide. While potassium phthalimide was hydroxyethylated, sodium saccharin was not. The results are summarized in Table I.



The dissociation constants of phthalimide,[8] succinimide,[9] and saccharin,[10] which were hydroxyethylated in good yield, are 1.09×10^{-7}, 3.0×10^{-11} and 2.5×10^{-2} respectively (25°) and those of acetamide,[11] benzamide,[12] and acetanilide[13] which were not hydroxyethylated are 8.3×10^{-15}, *ca.* 1×10^{-14} and *ca.* 1×10^{-13}, respectively. Imides whose dissociation constants are larger than 10^{-11} – 10^{-12}, seem to be hydroxyethylated by ethylene carbonate.

EXPERIMENTAL

The mixture of imide and ethylene carbonate was heated under the conditions shown in Table I. The reaction products were treated as follows:

The reaction product of phthalimide and ethylene carbonate was recrystallized from water, m.p. 127°. The mixed melting point of this with *N*-2-hydroxyethylphthalimide was 126–127°. The infrared spectra of the two coincided.

The reaction product of potassium phthalimide with ethylene carbonate was washed with water and the precipitate was filtered. After it was treated with dilute hydrochloric acid, recrystallization from water gave N-2-hydroxyethylphthalimide. The mixed melting point of this with the authentic sample was 126–127°, and the infrared spectra of the two coincided.

The reaction product of naphthalimide and ethylene carbonate was recrystallized from water and N-2-hydroxyethylnaphthalimide was obtained, m.p. 172–173°.

Anal. Calcd. for $C_{14}H_{11}NO_3$: N, 5.80. Found: N, 5.99.

Distillation of the reaction product of succinimide with ethylene carbonate under vacuum gave N-2-hydroxyethylsuccinimide, b.p. 161–162° (3 mm. Hg), m.p. 62.5–63.5° (from acetone–carbon tetrachloride).

Anal. Calcd. for $C_6H_9NO_3$: C, 50.34; H, 6.34 N, 9.79. Found: C, 49.73; H, 6.53; N, 10.05.

Distillation of the reaction product of diacetamide with ethylene carbonate gave *N*-2-hydroxyethyldiacetamide, b.p. 129° (2.5 mm. Hg), 124° (1.5 mm.).

Anal. Calcd. for $C_6H_{11}NO_3$: N, 9.65. Found: N, 9.69.

The reaction product of saccharin with ethylene carbonate was recrystallized from water, and *N*-2-hydroxyethylsulfobenzimide was obtained, m.p. 105.5–106.5°.

Anal. Calcd. for $C_9H_9NO_4S$: C, 47.58; H, 3.99; N, 6.17. Found: C, 47.66; H, 3.54; N, 6.21.

DEPARTMENT OF SYNTHETIC CHEMISTRY
FACULTY OF ENGINEERING
KYUSHU UNIVERSITY
HAKOZAKI FUKUOKA, JAPAN

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(8) J. K. Wood, *J. Chem. Soc.*, **89**, 1831 (1906).

(9) J. K. Wood, *J. Chem. Soc.*, **89**, 1837 (1906).

(10) N. A. Lange, *Handbook of Chemistry*, 8th ed., Handbook Publishers, Inc., Sandusky, Ohio (1952), p. 1229.

(11) G. E. Branch and J. O. Clayton, *J. Am. Chem. Soc.*, **50**, 1685 (1928).

(12) G. E. Branch and J. O. Clayton, *J. Am. Chem. Soc.*, **50**, 1686 (1928).

(13) C. G. Derick and J. H. Bormann, *J. Am. Chem. Soc.*, **35**, 1284 (1913).

Preparation of Halo-5-nitro-2-furanacrylanilides

ROBERT G. TABORSKY

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Several halo-5-nitro-2-furanacrylanilides have been reported as being effective anthelmintics and bacteriostats.[1–3] These compounds had been prepared by the reaction of purified 5-nitro-2-furanacryloyl chloride with a halogenated aniline under

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(1) K. Miura, M. Ikeda, and S. Yasuda, *J. Pharm. Soc. Japan*, **75**, 57 (1955).

(2) M. Ikeda, *J. Pharm. Soc. Japan*, **75**, 628 (1955).

(3) M. Ikeyoshi and T. Miura, Jap. Patent **3871** (1957).

TABLE I

HALO-5-NITRO-2-FURANACRYLANILIDES

Compound	M.P.,[a] °C.	Formula	Analysis Carbon, % Calcd.	Analysis Carbon, % Found	Analysis Hydrogen, % Calcd.	Analysis Hydrogen, % Found	Yield,[b] %
2′-Chloro-5-nitro-2-furanacrylanilide	187(lit.[8] 188)	$C_{13}H_9ClN_2O_4$	53.34	53.58	3.09	3.03	72
3′-Chloro-5-nitro-2-furanacrylanilide	205.5–206(lit.[8] 201)	$C_{13}H_9ClN_2O_4$	53.34	53.75	3.09	3.05	89
4′-Chloro-5-nitro-2-furanacrylanilide	216(lit.[8] 214)	$C_{13}H_9ClN_2O_4$	53.34	53.56	3.09	3.14	76.5
2′,4′-Dichloro-5-nitro-2-furanacrylanilide	217.5–218	$C_{13}H_8Cl_2N_2O_4$	47.71	48.05	2.46	2.49	
4′-Bromo-5-nitro-2-furanacrylanilide	230.5–231(lit.[8] 222)	$C_{13}H_9BrN_2O_4$	46.31	47.56	2.69	2.34	77.1

[a] Of material crystallized once from ethanol; the melting point was determined on a Fisher metal block melting point apparatus calibrated against standards. [b] Of uncrystallized material, which in each case melted over less than a 3° range (based on the amount of 5-nitro-2-furanacrylic acid used).

anhydrous conditions, in the presence of large amounts of copper shot.[3]

In the present work, the preparation of these compounds has been further studied and two procedures which are more convenient and more economical than the above method have been developed.

Attempts induce ethyl 5-nitro-2-furanacrylate to react with *p*-chloroaniline under a variety of conditions failed to produce the desired anilide. In a second method, 5-nitro-2-furanacrylic acid, *p*-chloroaniline, and phosphorus trichloride reacted in benzene to give a 65% yield of 4′-chloro-5-nitro-2-furanacrylanilide.

In a third procedure studied, a Schotten-Baumann procedure was found to be a very successful route to the anilides under study. It was found that the acid chloride preparation mixture could be treated directly with halogenated anilines, in the presence of aqueous base, to give a good yield of pure anilide which could be filtered directly from the reaction mixture.

5-Nitro-2-furanacrylic acid has been previously prepared by a Perkin condensation of 5-nitrofurfural and acetic anhydride. However, upon attempting to prepare this acid in the present work, by a Knoevenagel condensation between malonic acid and 5-nitrofurfural, only tars were obtained. Therefore, the nitro acid was prepared by nitration of 2-furanacrylic acid in acetic anhydride.[4]

5-Nitro-2-furanacryloyl chloride was prepared with phosphorus pentachloride[5] or phosphorus trichloride, but thionyl chloride was not applicable. Ethyl 5-nitro-2-furanacrylate was prepared by the nitration of ethyl 2-furanacrylate[4] which was prepared by a Claisen condensation of furfural and ethyl acetate.[6]

The halo-5-nitro-2-furanacrylanilides prepared in the present work are presented in Table 1. 2′,4′-Dichloro-5-nitro-2-furanacrylanilides has not been previously prepared.

EXPERIMENTAL

Reagents. 2-Furanacrylic acid was purchased from the Eastman Kodak Co., Rochester, N. Y., and a sample of 5-nitrofurfural was obtained from the Norwich Pharmacal Co., Norwich, N. Y.

Ethyl 2-furanacrylate was prepared by the Claisen condensation from furfural and ethyl acetate[6] to give the desired ester, b.p. 111–114°/10 mm. which was redistilled at 97–99°/4 mm. (lit.[7] b.p. 120–121°/17 mm.).

Ethyl 5-nitro-2-furanacrylate was prepared by nitrating ethyl 2-furanacrylate in acetic anhydride[4] to give a pure product, m.p. 123.5–124° (lit.[4] m.p. 123°).

Halo-5-nitro-2-furanacrylanilides (attempts by ester-haloaniline reaction). Attempts were made to react ethyl 5-nitro-2-furanacrylate with *p*-chloroaniline by: (1) allowing a chloroform solution of the reactants to stand for 6 days at room temperature; (2) heating the mixture in refluxing xylene and allowing any alcohol formed to be driven off; (3) heating the mixture at 120° for 20 hr. in dimethylformamide. However, in all of these experiments only the starting reagents were recovered.

Halo-5-nitro-2-furanacrylanilides (by the phosphorus trichloride method). Four g. (0.02 mole) of 5-nitro-2-furanacrylic acid and 6.0 g. (0.05 mole) of *p*-chloroaniline were intimately ground, mixed, and refluxed with 1.5 ml. of phosphorus trichloride and 35 ml. of benzene for 16 hr. The mixture was cooled and filtered and the residue suspended into 10% hydrochloric acid, 10% sodium carbonate, re-filtered, and washed. Crystallization from ethanol gave 3.9 g. (65% yield) of 4′-chloro-5-nitro-2-furanacrylanilide, m.p. 213–215° (lit.[8] 214°). Admixture with the material prepared by the Schotten-Baumann reaction caused no depression of its melting point.

Halo-5-nitro-2-furanacrylanilide (by the Schotten-Baumann procedure). In initial work, the intermediate acid chlorides had been isolated. However, it was found that neither the purity nor the yield of the product was deleteriously affected if the acid chloride reaction mixture were reacted directly with the aniline. Either phosphorus pentachloride or phosphorus trichloride could be used to make the acid chloride. However, thionyl chloride was not found to be effective.

The method described below was used for the preparation of all of the compounds in Table 1.

One hundred g. (0.55 mole) of 5-nitro-2-furanacrylic acid, 167 g. of phosphorus pentachloride, and 1 l. of benzene were refluxed for 4 hr. This solution was diluted to 1160 ml. with benzene and 1067 ml. (equivalent to 0.51 mole of acid) were added over a 30-min. period to a rapidly stirred and cooled (ice) mixture of 100 g. (0.79 mole) of *p*-chloroaniline dissolved in 1300 ml. of benzene and 520 g. of sodium hydroxide

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(4) H. Gilman and G. F. Wright, *J. Am. Chem. Soc.*, **52**, 2550 (1930).

(5) K. Matsumoto, R. Ueno, and M. Ueno, Jap. Patent 2667 (1950).

(6) H. Gilman, R. E. Brown, and H. L. Jones, *Iowa State Coll. J. Sci.*, **2**, 317 (1928).

(7) I. Heilborn and H. M. Burnsbury, *Dictionary of Organic Compounds*, Eyre and Spottiswoode, London, 1953, p. 575.

(8) T. Takahoshi, H. Saikachi, S. Yoshima, and C. Mizuno, *J. Pharm. Soc. Japan*, **69**, 286 (1949).

dissolved in 2500 ml. of water. The mixture was stirred for 30 min. more and vacuum-filtered. The residue was suspended into 10% hydrochloric acid, refiltered, and washed with water to give, upon drying, 114 g. (76.5% yield) of 4′-chloro-5-nitro-2-furanacrylanilide, m.p. 212–213.5° (lit.,[8] m.p. 214°). A portion was crystallized from alcohol to give orange crystals, m.p., 216°.

Anal. Calcd. for $C_{13}H_9ClN_2O_4$: C, 53.34; H, 3.09. Found: C, 53.56; H, 3.14.

BEN VENUE LABORATORIES, INC.
BEDFORD, OHIO

Dienone-Phenol Rearrangement of 2-Phenyl-*o*-quinolacetate[1]

H. BUDZIKIEWICZ AND W. METLESICS

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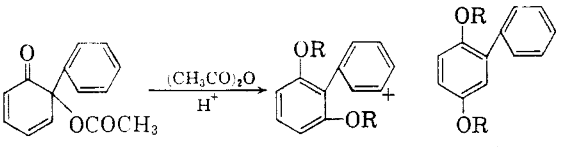
In preceding papers[2,3] it has been shown that *o*-quinol acetates, when treated with acetic anhydride and a catalytic amount of concentrated acid or BF_3-etherate, are readily rearranged to acetylated phenols.

Under these conditions 2-methyl-*o*-quinol acetate yields 85% of 2,6-diacetoxytoluene and a trace of 2,5-diacetoxytoluene. In analogy to this result we expected to get mainly 2,6-diacetoxybiphenyl by subjecting 2-phenyl-*o*-quinol acetate (I) to this reaction:



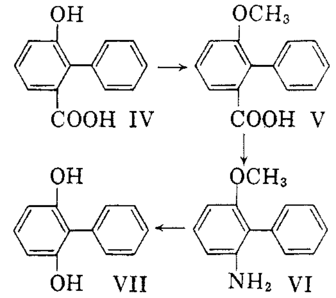
I II III
a. R = CH_3CO a. R = CH_3CO
b. R = H b. R = H

From the crude product an acetate, m.p. 91–93°, was obtained in 90% yield. Hydrolysis gave a phenol, m.p. 117–119°.

These melting points differ greatly from the figures given by Kubota and his co-workers[4] who described 2,6-dihydroxybiphenyl as having a melting point of 138° (m.p. of the diacetate 111°), a substance which we can hardly believe to be identical with our phenol IIb.

As infrared absorption, chromatographic behavior, and color reactions are consistent with the assumed structure of II, we have secured this result by an independent synthesis.

6-Hydroxybiphenyl-2-carboxylic acid (IV)[5] was transformed into 2,6-dihydroxybiphenyl as shown in the illustrated scheme.



The resulting phenol was identical with our rearrangement product IIb, as shown by mixed melting point and paper chromatography.

In the mother liquor of IIb some trace of a second phenol was found by paper chromatography. Color reaction and R_f value were the same as observed with a sample of 2,5-dihydroxybiphenyl[6] which had been prepared for comparison.

EXPERIMENTAL[7]

2-Phenyl-o-quinol acetate, I, was prepared by lead tetraacetate oxydation of 2-hydroxybiphenyl according to the directions of Wessely and his co-workers.[8]

Rearrangement of 2-phenyl-o-quinol acetate, I. Two-tenths of a gram of I was added in portions while stirring to a mixture of 2 ml. acetic anhydride and 2 drops of perchloric acid. The mixture was allowed to stand for 2 hr., then it was poured into 20 ml. of water. Having thus stood during the night, crystals had separated in 90% yield. The analytical sample, which was recrystallized from methanol and a mixture of ether and ligroin, resulted in 2,6-diacetoxybiphenyl, IIa, m.p. 91–93°, $\gamma_{\max}^{CS_2}$ 1770 (C=O), 734, 696 (monosubstituted benzene ring), 762 (1,2,3-trisubstituted benzene ring).

Anal. Calcd. for $C_{16}H_{14}O_4$: C, 71.1; H, 5.2. Found: C, 71.3; H, 5.4.

Hydrolysis of the crude rearrangement product with a mixture of 10% sulfuric acid and methanol (1:1) yielded crystals which were recrystallized to give 2,6-dihydroxybiphenyl, IIb, m.p. 117.5–119°. IIb with an ethanolic solution of ferric chloride did not show any color reaction.

Anal. Calcd. for $C_{12}H_{10}O_2$: C, 77.4; H, 5.4. Found: C, 78.0; H, 5.5.

Paper chromatography of the products of hydrolysis was carried out by descending the upper phase of a mixture of benzene, glacial acetic acid, and water (4:1:5). IIb having been sprayed with diazotized sulfanilic acid solution and treated with ammonia vapors, formed a reddish brown spot. The mother liquors of IIb showed a second spot with the same R_f value and color reaction as observed with a sample of *2,5-dihydroxybiphenyl,* IIIb.

2,6-Dihydroxybiphenyl, VII, has been synthesized as follows:

6-Methoxybiphenyl-2-carboxylic acid, V. 6-Hydroxybiphenyl-2-carboxylic acid, IV,[5] treated with dimethylsulfate

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[1] Paper III on Dienone-Phenol-Rearrangement of Quinols.

[2] F. Wessely and W. Metlesics, *Monatsh. Chem.*, **85**, 637 (1954).

[3] W. Metlesics, F. Wessely, and H. Budzikiewicz, *Tetrahedron*. . . . (1959).

[4] B. Kubota, Y. Fujimura, K. Akashi, *Sci. Papers Inst. Phys. Chem. Research (Tokyo)*, **2**, 185 (1925); *Chem. Abstr.*, **19**, 2334 (1925).

[5] C. Graebe, P. Schestakow, *Ann.*, **284**, 316 (1894).

[6] W. Borsche, *Ann.*, **312**, 221 (1900).

[7] Infrared spectrum was measured using a Perkin-Elmer Model 21 spectrophotometer. Maxima are expressed in cm.$^{-1}$ Melting points are determined on a Kofler micro hot stage.

[8] F. Wessely, L. Holzer, and H. Vilcsek, *Monatsh. Chem.*, **83**, 1253 (1952).