[CONTRIBUTION FROM THE FRICK CHEMICAL LABORATORY, PRINCETON UNIVERSITY, AND THE NOYES LABORATORY OF CHEMISTRY, UNIVERSITY OF ILLINOIS]

Some Further Reactions of α-Cyanobenzyl Benzenesulfonate[1]

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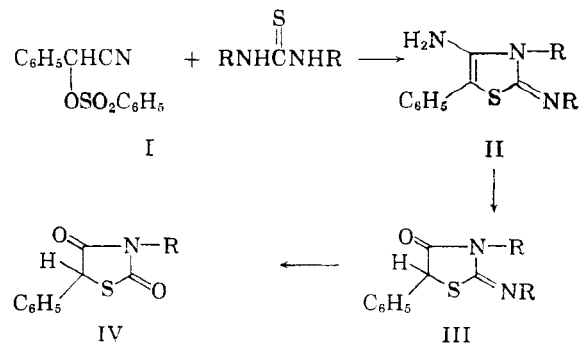
The condensation of α-cyanobenzyl benzenesulfonate with *sym*-disubstituted thioureas, 2-imidazolidinethione (ethylenethiourea), 2-mercapto-4,6-diaminopyrimidine, and *o*-aminothiophenol to give thiazoles and condensed thiazole systems is described. Reaction of I with liquid ammonia gives benzamide in quantitative yield and constitutes a potentially useful method for the oxidation of an aldehyde to the corresponding acid without the use of conventional oxidizing agents. Reaction of I with sodium ethoxide yields ethyl benzoate and α-cyanobenzyl phenyl sulfone, while reaction with sodium cyanide in ethanol gives ethyl benzoate and *trans*-dicyanostilbene. The latter product is also formed in small amount in the condensation of I with ammonium hydroxide and with sodium hydroxide to give benzamide and sodium benzoate respectively. The mechanisms of these reactions are discussed.

Although α-halocyanohydrins have been extensively investigated, comparatively little is known about the closely related arylsulfonate esters of cyanohydrins. The only derivatives of this type which appear thus far to have been reported are the arylsulfonate esters of the cyanohydrins formed from benzaldehyde,[3-8] α-phenylacetaldehyde,[7] β-phenylpropionaldehyde,[7] formaldehyde,[8] propionaldehyde,[8] trichloroacetaldehyde,[8] and some substituted benzaldehydes.[9] Attention has thus far been focused primarily on the chemistry of α-cyanobenzyl arylsulfonates, both because of their facile formation from benzaldehyde, sodium cyanide, and arylsulfonyl chlorides, and because of their considerable reactivity. The reactions of these materials parallel to some extent those of the corresponding α-halonitriles,[7] but they do not possess the extremely disagreeable physical characteristics of the latter derivatives. The reactions of α-cyanobenzyl benzenesulfonate with sulfonyl chloride and thiourea to give α-cyanobenzyl aryl (or alkyl)sulfones,[4,7,10] with sodium cyanide and benzaldehyde to give 2,5-diphenyloxazole,[4] with thioureas,[4,5] dithiocarbamates,[6] and thioamides[11] to give thiazoles, with aromatic hydrocarbons under Friedel-Crafts conditions to give diarylacetonitriles[12] and the reaction of α-cyanobenzyl toluene-*p*-sulfonate with sodium ethoxide to give ethyl benzoate[9] have already been reported. We wish to report in this paper some further reactions of α-cyanobenzyl benzenesulfonate which were studied in an effort to extend the applicability of these simple carbonyl derivatives as synthetic intermediates.

sym-Disubstituted thioureas react in the same manner as monosubstituted thioureas[5] and yield 2-iminothiazole derivatives. Thus, the condensation of α-cyanobenzyl benzenesulfonate (I) with thiocarbanilide gave 2-phenylimino-3,5-diphenyl-4-thiazolidone (III. R = C_6H_5) as the first isolable product; the initially formed 4-amino derivative (II. R = C_6H_5) had apparently been hydrolyzed during the work-up. Extreme acidlability of such 4-aminothiazole derivatives has been noted previously.[5] The structure of III was confirmed by further hydrolysis to the known 3,5-diphenyl-2,4-thiazolidione (IV. R = C_6H_5).



1,3-Dibenzylthiourea reacted similarly with I to give the benzenesulfonate of 2-(3*H*)-benzylimino-3-benzyl-4-amino-5-phenylthiazole (II. R = —CH_2-C_6H_5). Addition of water to the ethanolic reaction mixture sufficed to hydrolyze the 4-amino group to give 2-benzylimino-3-benzyl-5-phenyl-4-

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(2) A part of this work is taken from theses presented by G. A. B. and N. A. G. to the University of Illinois in partial fulfillment of requirements for the B. S. degree.

(3) F. Francis and O. C. M. Davis, *J. Chem. Soc.*, **95**, 1403 (1909).

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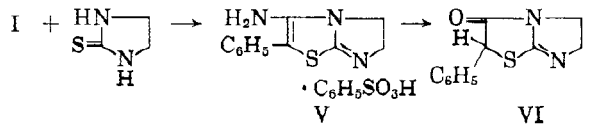
(11) E. C. Taylor, J. A. Anderson, and G. A. Berchtold, *J. Am. Chem. Soc.*, **77**, 5444 (1955).

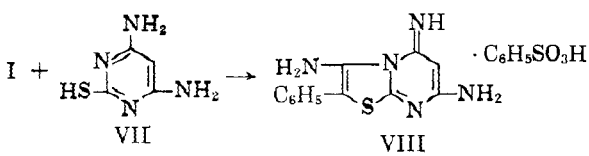
(12) K. Sisido, H. Nozaki, M. Nozaki, and K. Okano, *J. Org. Chem.*, **19**, 1699 (1954).

thiazolidone (III. R = $-CH_2C_6H_5$). Vigorous hydrolysis then gave 3-benzyl-5-phenyl-2,4-thiazolidione (IV. R = $-CH_2C_6H_5$). 2-Imidazolidinethione (ethylene thiourea) reacted in a similar fashion with I to give 2-phenyl-3-amino-5,6-dihydroimidazolo(2,1-b)thiazole benzenesulfonate (V). Hydrolysis of this compound yielded 2-phenyl-2,3,5,6 - tetrahydroimidazolo(2,1 - b)thiazolone-3 (VI).



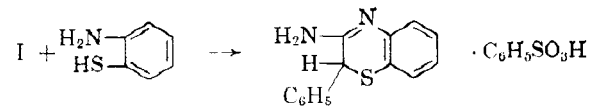
V VI

Attempts to extend these reactions to the preparation of fused pyrimidine heterocycles were only partially successful. Thus, the condensation of 2-mercapto-4,6-diaminopyrimidine (VII) with α-cyanobenzyl benzenesulfonate (I) in the presence of sodium iodide yielded the benzenesulfonate of 2 - phenyl - 3,6 - diamino - 4 - iminothiazolo(2,3-b)pyrimidine (VIII), but no reaction took place with thiouracil, and an unidentified, high melting



VII VIII

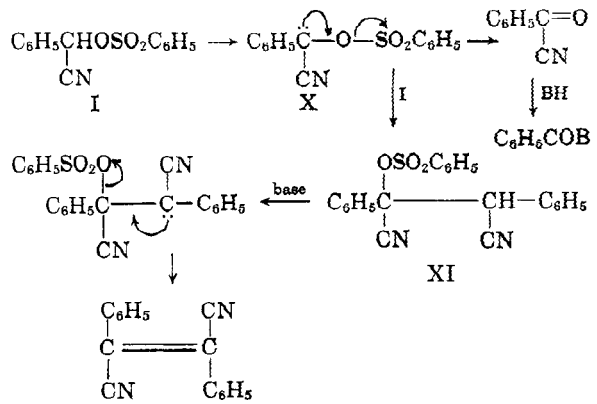
yellow solid was obtained upon attempted condensation with 2-thiobarbituric acid. However, compound I condensed smoothly and in high yield with *o*-aminothiophenol in the presence of sodium iodide to give 2-phenyl-3-amino-1,4-benzothiazine benzenesulfonate (IX).



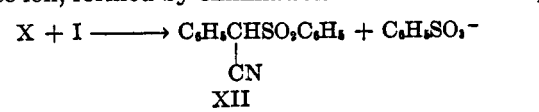
IX

The initial step in all of the reactions discussed thus far has been nucleophilic attack by sulfur on the benzyl carbon atom of α-cyanobenzyl benzenesulfonate with displacement of benzenesulfonate ion, followed by an intramolecular cyclization across the nitrile group of the resulting intermediate. The reaction of I with strong bases takes a different course. Here the initial step is removal of the acidic benzyl proton followed by elimination of *benzenesulfinate* ion to give benzoylcyanide, and the isolated products arise by reaction of this highly reactive intermediate with the base employed. Thus, the reaction of α-cyanobenzyl toluene-*p*-sulfonate with sodium ethoxide has been shown to give sodium toluene-*p*-sulfinate and ethyl benzoate.[9] We had found independently[2] that α-cyanobenzyl benzenesulfonate reacts with liquid ammonia to give ammonium benzenesulfinate and benzamide in quantitative yield. Concentrated ammonium hydroxide and 10% sodium hydroxide yield benzamide and sodium benzoate respectively. This reaction would seem to represent a potentially useful method for oxidizing an aldehyde to the corresponding acid without the use of conventional oxidizing agents.

In both of the latter two reactions, a small amount of *trans*-dicyanostilbene was isolated. The same product was also formed from an attempted condensation of guanidine carbonate with I in dimethylformamide solution. The reaction of I with sodium cyanide in ethanol yielded both *trans*-dicyanostilbene and ethyl benzoate. The formation of these products is readily explained by assuming that the initially formed anion (X) can (a) eliminate benzenesulfinate ion to give benzoyl cyanide, which can then react with solvent, or (b) displace benzenesulfonate ion from I to give XI, which can then, by the path pictured below, give rise to *trans*-dicyanostilbene. The low yield of the latter compound observed in these reactions is to be expected, as it is formed by a competitive reaction from the initially formed carbanion X. Furthermore, *trans*-dicyanostilbene arises only in the presence of weak bases, as its formation demands the presence in the reaction mixture of unchanged I.



It has already been reported that the reaction of α-cyanobenzyl toluene-*p*-sulfonate with an equimolar amount of sodium ethoxide yields ethyl benzoate and sodium toluene-*p*-sulfonate,[9] and that reaction with triethylamine yields a sulfone. On the other hand, the reaction of an excess of I with sodium ethoxide yields α-cyanobenzyl phenyl sulfone (XII), in addition to ethyl benzoate and sodium benzenesulfonate. The sulfone, which is also formed by the reaction of I with various amines (ethanolamine, hydrazine, semicarbazide hydrochloride, etc.) undoubtedly arises as previously suggested[9]; *i.e.*, by attack by benzenesulfinate ion, formed by elimination from the anion X,



XII

upon an unchanged molecule of I, with elimination of benzenesulfonate ion.

EXPERIMENTAL[13]

2-Phenylimino-3,5-diphenyl-4-thiazolidone (*III*. $R = C_6H_5$), A mixture of 5.5 g. of α-cyanobenzyl benzenesulfonate, 4.6 g. of thiocarbanilide, and 100 ml. of ethanol was warmed for a few minutes on a steam bath until complete solution had been achieved and then allowed to stand overnight at 0–5°. Filtration removed a part of the product; addition of water to the filtrate precipitated the remainder to give 5.4 g. (79%) of colorless crystals, m.p. 130–134°. Recrystallization from ethanol sharpened the melting point to 132–132.5°.

Anal. Calcd. for $C_{21}H_{16}N_2OS$: C, 73.2; H, 4.7; N, 8.1. Found: C, 73.0; H, 4.8; N, 8.0.

3,5-Diphenyl-2,4-thiazolidione (*IV*. $R = C_6H_5$). A solution of 2.0 g. of 2-phenylimino-3,5-diphenyl-4(5*H*)-thiazolidone in 50 ml. of 40% sulfuric acid was heated under reflux for 6 hr. and then cooled and filtered. The collected solid was recrystallized from ethanol to give 1.4 g. (90%) of colorless crystals, m.p. 172.5–173°. A mixed melting point with an authentic sample[5] of 3,5-diphenyl-2, 4-thiazolidione showed no depression.

2-Benzylimino-3-benzyl-5-phenyl-4-thiazolidone (*III*. $R = CH_2C_6H_5$). A mixture of 5.5 g. of α-cyanobenzyl benzenesulfonate, 5.1 g. of 1,3-dibenzylthiourea, and 100 ml. of absolute ethanol was heated for a few minutes until solution was complete and then chilled at 0–5° for 24 hr. Filtration yielded 4.8 g. of 2-(3*H*)-benzylimino-3-benzyl-4-amino-5-phenylthiazole benzenesulfonate as colorless crystals, m.p. 173–178°. The compound proved to be too unstable for recrystallization, however. The above preparation was therefore repeated, but water was added to the reaction mixture prior to filtration. Recrystallization of the solid so obtained from aqueous ethanol gave 5.5 g. (73%) of colorless crystals, m.p. 106–106.5°.

Anal. Calcd. for $C_{23}H_{20}N_2OS$: C, 74.3; H, 5.4; N, 7.5. Found: C, 74.15; H, 5.25; N, 7.3.

3-Benzyl-5-phenyl-2,4-thiazolidione (*IV*. $R = CH_2C_6H_5$). A solution of 4.0 g. of 2-benzylimino-3-benzyl-5-phenyl-4(5*H*)-thiazolidone in 60 ml. of 40% sulfuric acid was heated under reflux for 1 hr. and then cooled. The product separated as an oily layer. Addition of ice and filtration yielded a solid which was recrystallized from ethanol to give long, colorless needles, m.p. 81.5–82.5°; yield, 2.1 g. (69%).

Anal. Calcd. for $C_{16}H_{13}NO_2S$: C, 67.8; H, 4.6; N, 4.9. Found: C, 68.0; H, 4.9; N, 4.8.

2-Phenyl-3-amino-5,6-dihydroimidazolo(2,1-b)thiazole benzenesulfonate (V). A mixture of 10.9 g. of α-cyanobenzyl benzenesulfonate, 4.1 g. of 2-imidazolidinethione and 80 ml. of ethanol was allowed to stand at room temperature for 4 hr. A small amount of ether was added, and after 24 hr. the mixture was filtered to give 8.65 g. of solid. Evaporation of the filtrate yielded an additional 3.4 g. (total yield, 12.05 g., 80%). Recrystallization from ethanol gave colorless crystals, m.p. 206–207° dec.

Anal. Calcd. for $C_{17}H_{17}N_3O_3S_2$: C, 54.4; H, 4.5; N, 11.2. Found: C, 54.5; H, 4.6; N, 11.0.

2-Phenyl-2,3,5,6-tetrahydroimidazolo(2,1-b)thiazolone-3 (VI). This material was obtained upon recrystallizing the preceding compound from water until a constant melting point of 138–139° was obtained.

Anal. Calcd. for $C_{11}H_{10}N_2OS$: C, 60.55; H, 4.6; N, 12.8. Found: C, 60.3; H, 4.5; N, 12.7.

2-Phenyl-3,6-diamino-4-iminothiazolo(2,3-b)pyrimidine benzenesulfonate (VIII). A mixture of 5.5 g. of α-cyanobenzyl benzenesulfonate, 2.8 g. of 2-mercapto-4,6-diaminopyrimidine, 3.0 g. of sodium iodide, 45 ml. of ethanol, and 35 ml. of water was heated under reflux for 7 hr. The reaction mixture was then evaporated to dryness under reduced pressure and the residue suspended in ethanol-ether (1:1). Filtration yielded 3.5 g. (42%) of crude product in the form of yellow flakes, m.p. 200–203°. Recrystallization from aqueous ethanol raised the melting point to 203–204°.

Anal. Calcd. for $C_{18}H_{17}N_5O_3S_2$: C, 52.05; H, 4.1; N, 16.9. Found: C, 52.5; H, 4.3; N, 16.9.

2-Phenyl-3-amino-1,4-benzothiazine benzenesulfonate (IX). A mixture of 5.5 g. of α-cyanobenzyl benzenesulfonate, 2.5 g. of *o*-aminothiophenol, 3.0 g. of sodium iodide, and 50 ml. of 95% ethanol was heated under reflux for 17 hr. Addition of water and cooling resulted in the separation of a yellow solid which was collected by filtration and recrystallized from ethanol. The product was obtained in the form of yellow platelets, m.p. 238–239° dec.; yield, 7.2 g. (90%).

Anal. Calcd. for $C_{20}H_{18}N_2O_3S_2$: C, 60.3; H, 4.5; N, 7.0. Found: C, 60.5; H, 4.7; N, 7.1.

Reaction of α-cyanobenzyl benzenesulfonate with liquid ammonia. A mixture of 2.7 g. of α-cyanobenzyl benzenesulfonate and 50 ml. of liquid ammonia was stirred slowly in a Dry Ice-acetone bath for 2 hr. and then allowed to warm to room temperature. The residual solid was washed with cold water, the aqueous filtrate was evaporated to dryness and the residue extracted with ether. The water-insoluble material and the solid obtained by evaporation of the ether extract were combined to give 1.2 g. (quantitative) of benzamide, m.p. 125–127°, identical with an authentic sample.

The ether-insoluble material was dissolved in water and the *p*H adjusted to 4 with hydrochloric acid. The solid which separated was collected by filtration to give 1.0 g. (70%) of benzenesulfinic acid, identical with an authentic sample.

Reaction of α-cyanobenzyl benzenesulfonate with ammonium hydroxide. A mixture of 2.7 g. of α-cyanobenzyl benzenesulfonate and 50 ml. of concd. ammonium hydroxide was stirred at room temperature for 24 hr., and the solid which had separated was collected by filtration; yield 0.2 g. (17%), m.p. 158–160°. This was shown to be *trans*-dicyanostilbene by comparison with an authentic sample.[14]

Evaporation of the filtrate above to approximately 15 ml. and cooling gave 0.68 g. (57%) of benzamide, m.p. 127–128°, identical with an authentic sample. The filtrate was evaporated to dryness, the residue dissolved in ethanol and ether added to precipitate 1.37 g. of a mixture of ammonium benzenesulfonate and ammonium benzenesulfinate, as determined by a comparison of the infrared spectrum of the material with an authentic mixture.

Reaction of α-cyanobenzyl benzenesulfonate with 10% sodium hydroxide. A mixture of 5.5 g. of α-cyanobenzyl benzenesulfonate and 100 ml. of 10% sodium hydroxide was allowed to stand at room temperature for 1 week. Filtration gave 0.09 g. (4%) of *trans*-dicyanostilbene, m.p. 158–159°, identical with an authentic sample. Acidification of the filtrate then resulted in the separation of 2.0 g. (81%) of benzoic acid, m.p. 121°. Evaporation of the filtrate to approximately 25 ml. and cooling gave a small amount of benzenesulfinic acid, 83–84°, identical with an authentic sample.

Reaction of α-cyanobenzyl benzenesulfonate with sodium cyanide. A solution of 0.49 g. of sodium cyanide and 2.7 g. of α-cyanobenzyl benzenesulfonate in 100 ml. of ethanol was allowed to stand at room temperature overnight and then evaporated to dryness. Extraction of the residue with ether and evaporation of the ether gave an oily residue with suspended crystals. Filtration yielded 0.4 g. (35%) of *trans*-dicyanostilbene, m.p. 158–159°; the filtrate (0.7 g., 51%) was shown to be ethyl benzoate by comparison of its infrared spectrum with that of an authentic sample. The ether-insoluble material was shown to be a mixture of sodium

(13) All melting points are uncorrected. We are indebted for the microanalyses to Dr. Joseph F. Alicino, Metuchen, N. J.

(14) C. J. Timmons and S. C. Wallwork, *Chem. & Ind.*, 62 (1955).

benzenesulfonate and sodium benzenesulfinate by comparison of its infrared spectrum with that of an authentic mixture.

Reaction of α-cyanobenzyl benzenesulfonate with sodium ethoxide (2:1). A solution of 5.5 g. (0.02 mole) of α-cyanobenzyl benzenesulfonate in 20 ml. of ethanol containing 0.23 g. (0.01 mole) of sodium was allowed to stand at room temperature for 3 hr. The solid which had separated was then collected by filtration to give 1.7 g. of sodium benzenesulfonate, identical with an authentic sample. Evaporation of the filtrate under reduced pressure and distillation of the liquid residue gave 1.35 g. (97%) of ethyl benzoate, b.p. 210–212°. The residue from the distillation was dissolved in water and the *p*H adjusted to 4 with hydrochloric acid. Filtration then gave 1.0 g. (39%) of α-cyanobenzyl phenyl sulfone, m.p. 148–150°, identical with an authentic sample.[4]

PRINCETON, N. J.

[CONTRIBUTION FROM THE ORGANIC CHEMISTRY DEPARTMENT RESEARCH DIVISION, ABBOTT LABORATORIES]

Nitrosation and Diazonium Salt Coupling of Amadori Products

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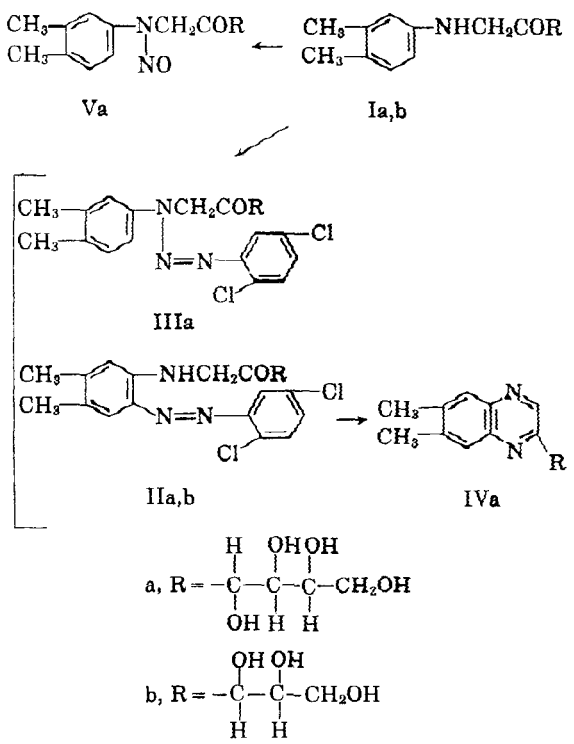
Whereas nitrosation of the aminodeoxyfructose derivative Ia occurs at the nitrogen atom, coupling with diazotized 2,5-dichloroaniline in aqueous acid solution takes place at the nitrogen and ring-carbon atoms. Coupling of the deoxypentulose derivative Ib occurs entirely at the ring-carbon atom. Attempts to convert the azo compounds IIa and IIb to analogs of riboflavin have failed. The structures of these Amadori products are discussed.

The present work was undertaken in an attempt to prepare an analog of riboflavin containing a 1-deoxy-D-erythropentulose side-chain in place of the normal D-ribityl group. It has been suggested[1] that this "dehydroriboflavin" may function as a biological precursor of the natural vitamin. This article describes unsuccessful efforts to synthesize it.

The 1-deoxy-D-fructose derivative Ia, in contrast to the structurally more pertinent Ib, is readily isolable.[1,2] Therefore, Ia was selected as a model. Coupling of Ia with diazotized 2,5-dichloroaniline[3] in aqueous acid solution gave two isomeric products: the yellow triazene IIIa and the red azo compound IIa, readily separated by fractional crystallization from 95% ethanol. The solubility, optical rotatory, and ultraviolet and infrared spectral properties of the triazene IIIa are quite similar to those recently reported by Kuhn, Krüger, and Seeliger[4] for a series of analogous compounds. However, under the basic conditions (pyridine-methanol) of their coupling reactions only the yellow triazenes were formed. Under the acidic conditions used in the present work, formation of the red azo compound IIa appeared to preponderate. Although it is much more soluble in ethanol than IIIa, IIa could be isolated readily in analytically pure form. Paper-strip chromatographic analysis demonstrated the absence in it of any of the yellow isomer (see Experimental).

Reductive cleavage of the azo group in IIa followed by condensation with alloxan gave no product possessing the properties of the desired isoalloxazine. This failure to react intermolecularly is accounted for by a predominant tendency of the intermediate *o*-phenylenediamine to cyclize to the quinoxaline IVa, identical with an authentic specimen prepared by treating 4,5-dimethyl-*o*-phenylenediamine with D-fructose, according to the method of Ohle.[5] Thus, little more was learned than that the preferred point of attack of the diazonium ion was at the symmetrical position of the benzene ring. This much was expected.[6]



(1) F. Weygand, *Ber.*, **73**, 1259 (1940).

(2) R. Kuhn and L. Birkofer, *Ber.*, **71**, 621 (1938).

(3) Preliminary experiments with a number of diazotized anilines demonstrated a clear superiority of this diazonium salt as regards yields and ease of purification of products.

(4) R. Kuhn, G. Krüger, and A. Seeliger, *Ann.*, **628**, 240 (1959).

(5) H. Ohle, *Ber.*, **67**, 155 (1934).