

anhydride and 25 ml. of acetyl chloride was refluxed gently for four hours, and then concentrated *in vacuo*. The 10-acetyl-3-chlorophenothiazine was obtained as a non-crystalline gum. The crude acetyl derivative, 50 ml. of acetic acid and 10 g. of 30% hydrogen peroxide were refluxed for four hours, and then concentrated *in vacuo*. The residual gum, 10-acetyl-3-chlorophenothiazine-5-oxide, was again non-crystalline. When this derivative, 25 ml. of 95% ethanol and 5 ml. of concentrated hydrochloric acid were refluxed for one hour, cooled and the solid filtered, there was obtained 8 g. (74% yield) of crude product, m.p. 270–273° dec.; pure 3-chlorophenothiazine-5-oxide, m.p. 280–281° dec., was obtained by recrystallization from aqueous dimethylformamide.

Anal. Calcd. for $C_{12}H_8ClNOS$: N, 5.61; Cl, 14.20. Found: N, 5.62; Cl, 14.26.

3-Chlorophenothiazine-5,5-dioxide.—Crude 10-acetyl-3-chlorophenothiazine, obtained as above from 24 g. of 3-chlorophenothiazine, was refluxed for four hours with 50 ml. of glacial acetic acid and 40 g. of 30% hydrogen peroxide. When the mixture was cooled, an oil separated which soon solidified. The solid was filtered and dried; it weighed 28 g. It consisted of a mixture of acetylated and deacetylated products. For identification a small portion of the crude material was extracted with boiling 95% ethanol and filtered hot; on cooling, the filtrate deposited crystals of 10-acetyl-3-chlorophenothiazine-5,5-dioxide, m.p. 167–168°.

Anal. Calcd. for $C_{12}H_8ClNO_2S$: C, 54.70; H, 3.61; N, 4.56. Found: C, 54.83; H, 3.50; N, 4.82.

The crude mixture was then hydrolyzed by refluxing for one hour with 24 ml. of concentrated hydrochloric acid and 500 ml. of 95% ethanol. The mixture was cooled, the solid filtered and recrystallized from aqueous dimethylformamide to give 22 g. (80% yield) of 3-chlorophenothiazine-5,5-dioxane, m.p. 295–297°.

Anal. Calcd. for $C_{12}H_8ClNO_2S$: C, 54.25; H, 3.04; N, 5.27. Found: C, 54.23; H, 3.23; N, 5.53.

3-Chloro-10-(2-dimethylamino-1-methylethyl)-phenothiazine-5,5-dioxide Oxalate.—A condensation was carried out as described above between 22 g. (0.066 mole) of 3-chlorophenothiazine-5,5-dioxide, 2.8 g. (0.07 mole) of sodium in 500 ml. of dry toluene and 80 ml. of 1 M solution of 2-chloro-N,N-dimethylpropylamine in toluene. The crude base, 30.5 g., was dissolved in 300 ml. of warm acetonitrile and treated with 7 g. of anhydrous oxalic acid in 70 ml. of warm acetonitrile. A gum separated from the cooled mixture. The acetonitrile was decanted, the gum was dissolved in 150 ml. of boiling water, the solution was decolorized with Darco, and filtered. The cooled filtrate deposited a solid which was filtered and recrystallized from acetonitrile to give 3.5 g. (10% yield), of product, m.p. 96–97° dec.

Anal. Calcd. for $(C_{17}H_{16}ClN_2O_2S)_2 \cdot C_2H_2O_4$: Cl, 8.96; N, 7.08. Found: Cl, 8.99; N, 7.09.

3-(1-Pyrrolidyl)-propyl Chloride.—No reference could be found to the preparation of this intermediate. To 250 g. (1.0 mole) of trimethylene chlorobromide in 250 ml. of dry ether was added, with stirring and ice cooling, 142 g. (2.0 moles) of pyrrolidine; an oil separated. The mixture stood overnight, the oil was separated and discarded; the ether layer was diluted with 250 ml. of ether, cooled in ice and extracted with three 250-ml. portions of ice-cold 10% hydrochloric acid. The hydrochloric acid extracts were cooled and made alkaline with 40% potassium hydroxide solution. The oil which separated was extracted with four 200-ml. portions of ether, the ether extracts were dried over anhydrous potassium carbonate, filtered, concentrated and distilled to give 97 g. (66% yield) of product, b.p. 103° (45 mm.).

Anal. Calcd. for $C_7H_{14}ClN$: N, 9.49; Cl, 24.01. Found: N, 9.29; Cl, 23.99.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, CARNEGIE INSTITUTE OF TECHNOLOGY]

The Benzidine Rearrangement. VI. The Rearrangement of 3,3',5,5'-Tetrafluorohydrazobenzene in 2:1 Sulfuric Acid¹

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When treated with 2:1 sulfuric acid at 85–90°, 3,3',5,5'-tetrafluorohydrazobenzene (I) yields the rearrangement products 2,2',6,6'-tetrafluorobenzidine (II), 2,2',4,6'-tetrafluorodiphenylene (III) and 2,2'-diamino-4,4',6,6'-tetrafluorobiphenyl (IV), plus the disproportionation products 3,5-difluoroaniline (V) and 3,3',5,5'-tetrafluoroazobenzene (VI). The relative amounts in which these products were formed are much less closely comparable with those in which analogous products were formed from 3,3',5,5'-tetrachloro-, -tetrabromo- and -tetramethylhydrazobenzenes than they are with the relative amounts in which corresponding products were formed from the rearrangement of unsubstituted hydrazobenzene under identical conditions. Since covalent fluorine is more like hydrogen than like chlorine in steric character, and more like chlorine than like hydrogen in its polar nature, the results of this investigation suggest that steric factors exert the major influence over product ratios when 3,3',5,5'-tetrasubstituted-hydrazobenzenes are rearranged, although other influences are also operative.

A comparison of the rearrangements of three 3,3',5,5'-tetrasubstituted-hydrazobenzenes in 2:1 sulfuric acid at 85–90° disclosed the fact that steric size of the substituent is a major but not the only factor which influences the ratio in which the three isomeric rearrangement products (benzidine, diphenylene and 2,2'-diaminobiphenyl) are formed.³ In order to gather additional information on the effects of 3,3',5,5'-tetrasubstitution on the ease of rearrangement, product ratios, extent of occurrence of the accompanying disproportionation ($2Ar-NHNHAr \rightarrow 2ArNH_2 + ArN=NAr$), and extent of formation of semidines, if any, the reactions of

3,3',5,5'-tetrafluorohydrazobenzene in 2:1 sulfuric acid have been studied and are reported in this article. The effects of the substituent fluorine were deemed likely to be especially significant in the effort to distinguish polar and steric effects of substituents; for in polar character fluorine more closely resembles the other halogens than it does hydrogen, whereas in steric size fluorine (van der Waals radius 1.35 Å.^{4,5}) more closely approaches hydrogen (1.2 Å.⁴) than it does the smallest of the other halogens (chlorine, 1.80 Å.⁴). Therefore, should the steric size of fluorine be the dominant factor governing the comparative behavior of 3,3',5,5'-tetrafluorohy-

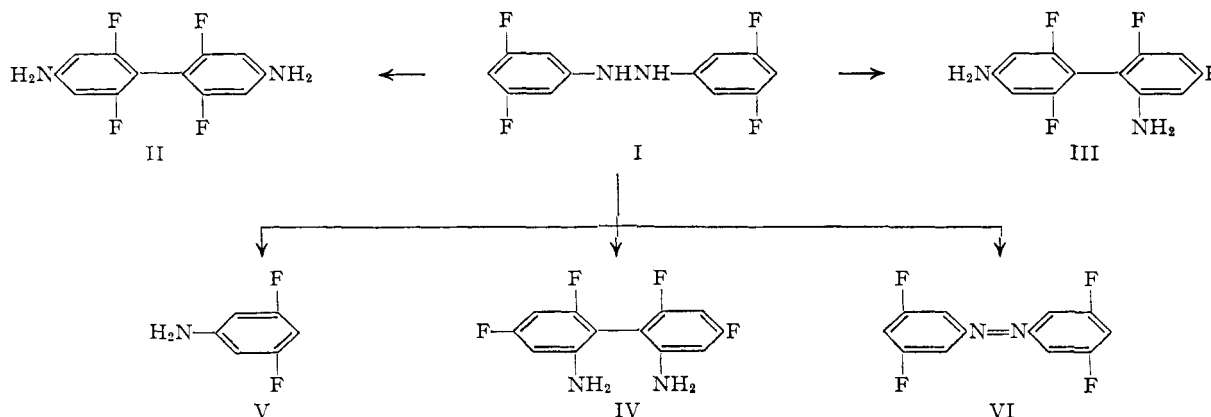
(1) From the D.Sc. Thesis by S. Allen Heininger.

(2) Plaskon Fellow, 1951–1952.

(3) R. B. Carlin and W. O. Forshey, Jr., *THIS JOURNAL*, **72**, 793 (1950).

(4) W. A. Waters, "Physical Aspects of Organic Chemistry," Fourth Ed., D. Van Nostrand Co., Inc., New York, N. Y., 1950, p. 58.

(5) H. P. Lemaire and R. L. Livingston, *J. Chem. Phys.*, **18**, 569 (1950).



drazobenzene, then its rearrangement should more closely resemble that of hydrazobenzene than that of the tetrachloro analog. On the other hand, if the polar character of fluorine is dominant, then a closer resemblance to the reactions of the tetrachlorohydrazobenzene should be observed. The rearrangement of the tetrafluorohydrazobenzene was carried out in 2:1 sulfuric acid at 85–90° in order that the results might be comparable with those of the preceding study,³ in which the same conditions were employed.

Following the completion of the work described in this paper, Bilbo and Wyman published the melting point, fluorine analysis and ultraviolet absorption spectrum of 2,2',6,6'-tetrafluorobenzidine (II), which they prepared by the reduction of 3,5-difluoronitrobenzene and subsequent treatment of the reduction product, presumably without isolating it, with tin and hydrochloric acid.⁶ Apparently they assumed without proof that their product was the substituted benzidine, rather than either of the two isomeric bases III or IV; and although experience with other 3,3',5,5'-tetrasubstituted-hydrazobenzenes³ makes such an assumption appear rather risky, it is shown to have been correct by the evidence of the investigation described here. 3,3',5,5'-Tetrafluorohydrazobenzene (I) was converted by the action of 2:1 sulfuric acid at 85–90° into a mixture of five products, and about 2.8% of unchanged I was recovered. The five products were isolated and separated in 88.1% yield (based on unrecovered I) by means of a complex separation procedure described in the Experimental section. The structures of the five products are shown in the accompanying formulations, and Table I

TABLE I

TRANSFORMATION PRODUCTS FROM 25.29 G. OF 3,3',5,5'-TETRAFLUOROHYDRAZOBENZENE IN 2:1 SULFURIC ACID

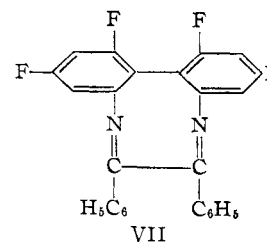
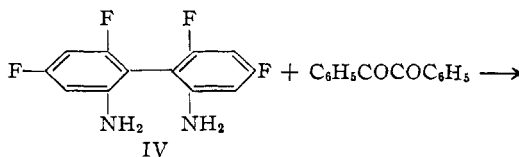
Product no.	Weight, g.	Yield, %
II	17.365	68.66
III	2.473	9.78
IV	0.540	2.14
V	0.965	3.81
VI	0.937	3.70
Total	22.280	88.09

gives the amounts of each which were isolated. Of the 11.9% of material for which no account is given

(6) A. J. Bilbo and G. M. Wyman, *THIS JOURNAL*, **76**, 5312 (1953).

in Table I, part of it was lost in the process of regenerating the tetrafluorobenzidine (II) from its difficultly soluble sulfate salt which separated from the reaction mixture, and the rest was isolated as a dark red, basic solid melting over a wide range which yielded no pure compounds and from which nothing could be distilled or sublimed in a high vacuum.

An indication that IV was the correct structure for the rearrangement product of I formed in smallest amount was derived from the observation that this isomer behaved as the least basic of the three in the countercurrent extraction procedure used to separate the mixture of isomers. In the separations of three isomeric rearrangement products from each of three other 3,3',5,5'-tetrasubstituted hydrazobenzenes by the same procedure, the isomer which in each case appeared as the least basic proved to be the 2,2'-diaminobiphenyl derivative.³ Essentially conclusive evidence supporting the 2,2'-diaminobiphenyl structure for this isomer was provided by the observation that IV reacted with equimolar amounts of benzil with the loss of two equivalents of water to form a crystalline, non-polymeric product which must have been 1,3,10,12-tetrafluoro-6,7-diphenyldibenzo[e,g][1,4]-diazocine (VII). Tauber⁷ has shown that 2,2'-diaminobiphenyl itself undergoes the same transformation. Neither a benzidine nor a diphenylene could form a monomeric condensation product of the same type with benzil. The ultraviolet extinction curve for

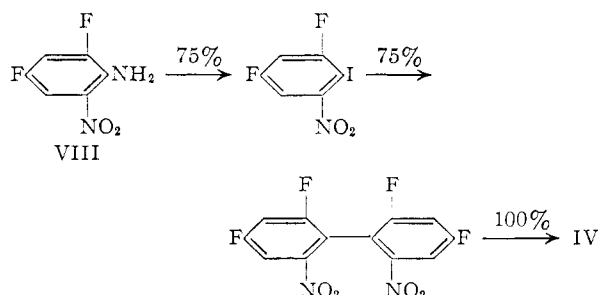


the rearrangement product of I formed in smallest amount also left little doubt that IV is its correct

(7) E. Tauber, *Ber.*, **25**, 3287 (1892).

structure (see below). However, IV could not be transformed into a carbazole derivative under conditions which convert 2,2'-diaminobiphenyl⁸ and its tetramethyl homolog³ into carbazole and tetramethylcarbazole, respectively.

Of the three isomeric rearrangement products, IV was the only one susceptible by reasonably accessible means to structure proof of the classical type. The method of structure proof which had been applied to the rearrangement products of the tetrachloro- and tetrabromohydrazobenzenes—namely, removal of halogen by hydrogenolysis and comparison of the products with known compounds—could not be adapted to the products of rearrangement of I. A synthesis of IV was achieved starting with 2,4-difluoro-6-nitroaniline (VIII), an intermediate in the synthesis of 3,5-difluoronitrobenzene and thence of I. A mixture of synthetic IV and a sample isolated from the rearrangement products of I showed no melting point depression.



The rearrangement product formed in largest amount was assigned the benzidine structure II by virtue of the following evidence. First, this compound formed a diacetyl and a bis-salicylal derivative; therefore two primary amino groups were present. Second, experience with the rearrangements of a large number of *para*-unsubstituted hydrazobenzenes has shown that whenever one product is formed in much larger amount than all others, that product has the benzidine structure.^{3,9} Third, like unsubstituted benzidine, II formed a sparingly soluble sulfate salt; the sulfates of its isomers, like those of the isomers of benzidine, did not separate from sulfuric acid solution. Fourth, in the course of separations of three isomeric rearrangement products from each of three other 3,3',5,5'-tetrasubstituted hydrazobenzenes by countercurrent extraction, the isomer which proved most basic in this procedure was the benzidine isomer³; the most basic of the three isomers from the rearrangement of I in the countercurrent extraction procedure was the one assigned the structure II.

The final and most persuasive argument favoring the benzidine structure II for the major rearrangement product of I is to be found in its ultraviolet extinction curve and in those for the other two rearrangement products. If the curves for unsubstituted benzidine, diphenylene and 2,2'-diaminobiphenyl were to be compressed toward shorter wave lengths, the compressed curves would be closely similar to those for their respective tetrafluoro analogs. The structures of the three rearrangement

products then become obvious in the light of this comparison.

In Table II the positions of the maxima and minima in the ultraviolet extinction curves for benzidine, diphenylene, 2,2'-diaminobiphenyl and their tetrafluoro derivatives are listed.

TABLE II
ULTRAVIOLET ABSORPTION DATA FOR REARRANGEMENT PRODUCTS OF 3,3',5,5'-TETRAFLUOROHYDRAZOBENZENE AND FOR THEIR UNSUBSTITUTED ANALOGS^a

Compound	$\lambda_{\max}$ (m μ)	log $\epsilon_{\max}$	$\lambda_{\min}$ (m μ)	log $\epsilon_{\min}$
Benzidine ^b	282-286	4.406	239	3.520
2,2',6,6'-Tetrafluoro-benzidine	262	4.455	228	3.882
Diphenylene ^b	240	4.228	285	3.770
	260 ^c	4.024 ^c		
	300	3.841		
2,2',4,6'-Tetrafluoro-diphenylene	241	4.410		
	279 ^c	3.869 ^c		
2,2'-Diaminobiphenyl	294	3.724	268	3.265
2,2'-Diamino-4,4',6,6'-tetrafluorobiphenyl	238	4.324	264	3.310
	285	3.683		

^a The ultraviolet spectra referred to in this paper have been deposited as Document number 4449 with the ADI Auxiliary Publication Project, Photoduplication Service, Library of Congress, Washington 25, D. C. A copy may be secured by citing the Document number and by remitting \$1.25 for photoprints, or \$1.25 for 35 mm. microfilm, in advance by check or money order payable to: Chief, Photoduplication Service, Library of Congress. ^b R. B. Carlin, R. G. Nelb and R. C. Odioso, *THIS JOURNAL*, **73**, 1002 (1951). ^c Shoulder.

The effect of fluorine atoms in the 2-, 2'-, 6- and 6'-positions on the ultraviolet absorption spectrum of benzidine has been considered in detail by Bilbo and Wyman,⁶ whose published melting point and ultraviolet extinction curve for the only tetrafluoro-diaminobiphenyl they mention having isolated agree very well with the properties of the major product from I obtained in the investigation reported here. The ultraviolet extinction curves for II, III and IV resemble those for benzidine, diphenylene and 2,2'-diaminobiphenyl, respectively, much more closely than they resemble the curves for the tetrachloro-, tetrabromo- and tetramethylbenzidines, diphenylenes and 2,2'-diaminobiphenyls, all of which have been found³ to be similar to the curve for aniline. This relationship among the spectra is subject to facile explanation in terms of the effect of steric size of *ortho* substituents on the approach to coplanarity of biphenyl rings.^{3,6} Because fluorine is somewhat larger in size than hydrogen but much smaller than chlorine, bromine or methyl, *ortho*-fluorine might be expected to offer some resistance to ring coplanarity but not nearly as much as is offered by the other three groups.

The third rearrangement product of I could have no other structure than III if the assignments of structures II and IV were correct and if the third product has two primary amino groups. The fact that two primary amino groups were present was demonstrated when the compound formed a diacetyl and a bis-salicylal derivative. The ultraviolet extinction curve for this product constitutes powerful positive evidence supporting its formulation as III; and the fact that it, like other tetrasubstituted

(8) E. Tauber, *Ber.*, **24**, 200 (1891); **26**, 1703 (1893).

(9) Cf. P. Jacobson, *Ann.*, **428**, 76 (1922).

diphenylenes, was of intermediate basicity between a benzidine and a 2,2'-diaminobiphenyl in the countercurrent extraction procedure provided additional evidence leading to the same conclusion.

The isolation of 3,5-difluoroaniline (V) and 3,3',5,5'-tetrafluoroazobenzene (VI) in effectively equal amounts from the products of the reaction of I with sulfuric acid shows that direct oxidation of I to VI could not have occurred to an appreciable extent; obviously these products are the result of disproportionation of I. Their identities were established by comparison with known specimens.

Discussion

A comparison of the relative amounts of the five products formed from I with data from the investigations of the reactions of the analogous tetrachloro-, tetrabromo- and tetramethylhydrazobenzenes under identical conditions³ reveals that I has in this respect behaved in a manner grossly different from the other three, all of which gave similar product ratios. The tetrafluorohydrazobenzene (I) yields relatively much more benzidine, much less diphenylene and 2,2'-diaminobiphenyl, and engages in disproportionation to a markedly smaller degree compared to the other three tetrasubstituted hydrazobenzenes. Because a comparison of I and unsubstituted hydrazobenzene should provide valuable information, the rearrangement of hydrazobenzene was carried out in 2:1 sulfuric acid at 85–90°, and the products were isolated and separated. The most reliable information from three runs accounts for products in 94.5% yield as follows: benzidine, 78.6%; diphenylene, 10.5%; azobenzene and aniline, both 2.7%. No 2,2'-diaminobiphenyl was isolated, but obviously a small amount could have escaped detection had it been formed. Thus, with respect to the relative rates of formation of products both of rearrangement and of disproportionation in 2:1 sulfuric acid at 85–90°, I resembles hydrazobenzene much more closely than it does any of the other three tetrasubstituted hydrazobenzenes. Therefore, on the basis of information now available, it seems safe to conclude that the relative rates of formation of rearrangement products and of disproportionation products of 3,3',5,5'-tetrasubstituted-hydrazobenzenes are controlled in large measure by the steric size of the substituents; such factors as medium effects and the polar nature of the substituents play significant but comparatively minor roles.

No measure of the total rates of rearrangement of I or of tetrachloro-, tetrabromo- or tetramethylhydrazobenzene has been carried out. Although qualitative observation has suggested that the tetramethyl derivative rearranges most rapidly of the group in 2:1 sulfuric acid at 85–90°, hydrazobenzene and I somewhat less rapidly, and the tetrachloro and tetrabromo compounds comparatively sluggishly, no conclusions concerning the effects of 3-, 3'-, 5- and 5'-substituents on the absolute rates of rearrangements of hydrazobenzenes can be drawn safely until quantitative information is at hand.

Finally, it should be noted that no compound having the properties of a semidine could be isolated from the products of I. Very small quantities

of a substance which may have been a semidine were isolated from the rearrangement products of 3,3',5,5'-tetrabromohydrazobenzene³; if this compound was indeed a semidine, it is the only one isolated in this series of investigations.

Experimental

3,3',5,5'-Tetrafluoroazobenzene (VI) and 3,3',5,5'-Tetrafluorohydrazobenzene (I).—A vigorously stirred suspension of 15.9 g. of 3,5-difluoronitrobenzene¹⁰ and 23 g. of zinc dust in 100 ml. of ethanol was heated to the boiling point and treated with 55 ml. of 30% aqueous sodium hydroxide at such a rate that vigorous boiling continued without external heating. A red solid separated from solution after the addition of about half of the alkali, but it redissolved as addition of the base was continued. About 75% of the ethanol was distilled from the product mixture, which was then diluted with 100 ml. of water, cooled and filtered. The product was separated from the sludge by repeated extractions with boiling ethanol, and the ethanol extracts were then concentrated to about 100 ml. When cooled the solution deposited 2.0 g. (16%) of orange needles, m.p. 83.5–86°. This tetrafluoroazobenzene (VI) yielded long, bright orange needles, m.p. 88.5–89°, after two recrystallizations from ethanol.

Anal. Calcd. for $C_{12}H_8N_2F_4$: C, 56.71; H, 2.36. Found: C, 56.98; H, 2.34.

The ultraviolet absorption spectrum of VI had a sharp band, λ_{max} 224 m μ , log ϵ_{max} 3.98 and a broad band, λ_{max} 315 m μ , log ϵ_{max} 4.26.

The filtrate from crude VI was heated to the boiling point and treated first with 5 ml. of glacial acetic acid and then with successive small portions of zinc dust until further additions caused no more fading of the color of the solution. The zinc dust was removed by a rapid filtration, and the light yellow solution was poured quickly with stirring into 1 l. of hot water. After the mixture was cooled, 9.1 g. (78%) of yellowish tetrafluorohydrazobenzene (I) was collected by filtration and dried over phosphorus pentoxide in a vacuum desiccator. This material was rearranged without further purification. The m.p., taken in the normal way, was 106–110°, and after repeated recrystallizations from petroleum ether, I formed tan crystals melting no higher than 109–112°. This same recrystallized material, however, melted instantly when plunged into a bath at 114°; at 113° ten seconds were required to liquefy a sample, and at 112° 50 seconds were required. The sample prepared for analysis was recrystallized from carbon tetrachloride; it comprised thick, pale yellow needles, m.p. 114° (10 sec.).

Anal. Calcd. for $C_{12}H_8N_2F_4$: C, 56.27; H, 3.12. Found: C, 56.03; H, 3.23.

The ultraviolet absorption spectrum of I is characterized by a maximum at 246 m μ (log ϵ 4.41) and a shoulder with an inflection at 274 m μ (log ϵ 3.60).

Reaction of 3,3',5,5'-Tetrafluorohydrazobenzene (I) with 2:1 Sulfuric Acid.—With vigorous stirring, 26.0 g. of finely ground I was added in small portions to 550 ml. of 2:1 (by weight) sulfuric acid which was heated to 85–90°, and the mixture was stirred and maintained in the same temperature range for three hours. Solid lumps were crushed from time to time as they formed.

Separation of the Products of Interaction of 3,3',5,5'-Tetrafluorohydrazobenzene (I) in 2:1 Sulfuric Acid. A. From Insoluble Solids.—The cooled rearrangement mixture was filtered through a sintered glass funnel, and the tan solid (23.83 g.) was washed well with water and dried over phosphorus pentoxide in a vacuum desiccator. The dried solid was extracted with ether; the residue after extraction was a tan powder weighing 22.18 g. Removal of the ether from the extract left an orange solid which was dissolved in 30 ml. of hot ethanol. Slow cooling of this solution caused the separation of 0.937 g. (3.70%) of 3,3',5,5'-tetrafluoroazobenzene (VI) in the form of long, orange needles, m.p. 86°. Concentration of the ethanol filtrate from VI yielded 0.71 g. of unchanged I; therefore, no more than 25.29 g. of I had been transformed to other products, and all reported yields are based on this figure.

(10) G. C. Finger, F. E. Reed and J. L. Finnerty, *THIS JOURNAL*, **73**, 153 (1951).

The tan, ether-insoluble solid was boiled with 20% aqueous sodium hydroxide for 30 minutes, the mixture was cooled, and 15.64 g. (61.84%) of tan, solid 2,2',6,6'-tetrafluorobenzidine (II), m.p. 157–163°, was collected by filtration and washed thoroughly with water. If the ether-insoluble solid was the sulfate salt of II ($[\text{benzidine H}_2]^{++}\text{SO}_4^{--}$), the recovery of II from the salt was effected in 97.7% yield. The salt could not have been the benzidine bisulfate ($[\text{benzidine H}_2]^{++}2\text{HSO}_4^-$) for this salt could not have yielded so much base II. A 1 g. sample of II was purified by allowing its solution in 1 l. of boiling water to cool slowly. The long, white needles which separated had the m.p. 165–166°. Bilbo and Wyman⁶ reported the same m.p.

Anal. Calcd. for $\text{C}_{12}\text{H}_8\text{N}_2\text{F}_4$: C, 56.27; H, 3.12. Found: C, 56.39; H, 3.22.

The N,N'-diacetyl derivative of II was prepared in quantitative yield by warming a sample of II with excess acetic anhydride on the steam-bath for 10 minutes. The solution was poured into water and the white solid product, after recrystallization from dilute ethanol, had the m.p. 300–301°.

Anal. Calcd. for $\text{C}_{16}\text{H}_{12}\text{N}_2\text{O}_2\text{F}_4$: C, 56.47; H, 3.56. Found: C, 56.42; H, 3.72.

The N,N'-bis-salicylal derivative of II was prepared in 89% yield by warming 0.1 g. of II with 2 ml. of salicylaldehyde on the steam-bath for 30 minutes. The yellow-orange solid mixture was dissolved in hot benzene, and the derivative crystallized from the hot solution when it was diluted with petroleum ether (b.p. 65–110°). Recrystallization from benzene-petroleum ether afforded short yellow needles, m.p. 274–275°.

Anal. Calcd. for $\text{C}_{26}\text{H}_{16}\text{N}_2\text{O}_2\text{F}_4$: C, 67.24; H, 3.48. Found: C, 67.17; H, 3.60.

B. From Product Solution.—The acid filtrate from the reaction mixture was cooled to 0°, made basic by treatment with 40% aqueous sodium hydroxide, and the alkaline mixture was steam distilled to remove 3,5-difluoroaniline (V). The distillate was saturated with sodium chloride and extracted with two portions of ether. The ether solution was treated with 15 ml. of acetic anhydride, the ether was removed by distillation, and the residue was poured into water. The dried white solid 3,5-difluoroacetanilide (1.275 g., m.p. 120–125°) was equivalent to 0.965 g. (3.81%) of V. Recrystallization from aqueous ethanol gave small white needles of V, m.p. 128–129°. The reported m.p. is 129–129.5°.¹⁰ A sample of 3,5-difluoroacetanilide was prepared by reducing 3,5-difluoronitrobenzene¹⁰ in acetic anhydride solution at room temperature under about two atmospheres pressure of hydrogen in the presence of Raney nickel. The solution after being filtered free of the catalyst was poured into water, and the solid product, following two sublimations at 0.01 mm. pressure and a recrystallization from dilute ethanol, had the m.p. 128.5–129°, alone or when mixed with a sample from the sulfuric acid treatment of I. The ultraviolet absorption spectrum showed a single maximum at 243 μ ($\log \epsilon$ 4.19).

The alkaline residue from the steam distillation of V was cooled and extracted with two portions of benzene, and the dark brown benzene solution was dried over potassium carbonate. Removal of the benzene left 5.99 g. of a red-brown oil in which some crystalline material formed after several hours. This material was partitioned through nine separatory funnels (no. 11–19), each of which contained 75 ml. each of benzene and 0.8 N aqueous hydrochloric acid. After distribution of the mixture through the nine separatory funnels, the material in each funnel was isolated by making the aqueous layer alkaline with sodium hydroxide and extracting all of the organic substances into the benzene layer, which was dried over potassium carbonate and evaporated to dryness. The oily materials from funnels 11, 12 and 13 were combined and repartitioned, using the same solvents, through five separatory funnels (no. 21–25). The oily materials from funnels no. 18 and 19 were combined and repartitioned through five funnels (no. 31–35) each of which contained 75 ml. each of benzene and 0.5 N aqueous hydrochloric acid. The dark oils from funnels 21 and 22 were combined and redistributed through five more funnels (no. 41–45) each of which contained 75 ml. each of benzene and 1.5 N hydrochloric acid. Following these four counter-current distributions, the crystalline solid fractions from funnels 14, 15, 16, 17, 23, 24, 25, 31, 32 and 33 (total weight

2.06 g.) were combined and sublimed at 100° (0.01 mm.). The sublimate comprised 1.81 g. of a white solid, m.p. 122–128°. This crude 2,2',4,6'-tetrafluorodiphenylene (III) was purified by another vacuum sublimation, one recrystallization from benzene-petroleum ether (b.p. 65–110°) and another from aqueous ethanol. The pure product formed tiny white needles, m.p. 135–136°.

Anal. Calcd. for $\text{C}_{12}\text{H}_8\text{N}_2\text{F}_4$: C, 56.27; H, 3.12. Found: C, 56.07; H, 3.15.

The N,N'-diacetyl derivative of III was prepared by bubbling a stream of ketene into an ether solution of III. Removal of the ether and treatment of the residue with aqueous ethanol yielded a tan solid, m.p. 212–215°, in 73% yield. A sublimation at 150° (0.01 mm.) and three recrystallizations from aqueous ethanol afforded white needles, m.p. 215–216°.

Anal. Calcd. for $\text{C}_{16}\text{H}_{12}\text{N}_2\text{O}_2\text{F}_4$: C, 56.47; H, 3.56. Found: C, 56.66; H, 3.77.

The N,N'-bis-salicylal derivative of III was prepared in 78% yield by the procedure used to prepare the analogous derivative of II. The derivative of III separated from a hot solution of the reaction mixture in 4 ml. of petroleum ether (b.p. 65–110°). The derivative formed bright yellow needles, m.p. 197–198°, after two recrystallizations from benzene-petroleum ether.

Anal. Calcd. for $\text{C}_{26}\text{H}_{16}\text{N}_2\text{O}_2\text{F}_4$: C, 67.24; H, 3.48. Found: C, 67.04; H, 3.53.

The dark oils from separatory funnels no. 34 and 35 (total weight 1.94 g.) were distilled at 100° (0.01 mm.). The tan solid distillate (1.725 g.) was sublimed in vacuum again and then recrystallized from water, from which it formed white needles of the tetrafluorobenzidine II, m.p. 165–166°, alone or when mixed with a sample made by alkali treatment of the insoluble sulfate salt. The total yield of II was therefore 17.365 g. (68.66%).

The semi-crystalline material from separatory funnel no. 41 (0.69 g.) yielded 0.54 g. (2.14%) of a yellowish solid, m.p. 97–98° after preliminary softening, when it was subjected to sublimation at 40° (0.01 mm.) for three days. A mixture of this material with a specimen of 2,2'-diamino-4,4',6,6'-tetrafluorobiphenyl (IV), m.p. 100–101°, which had been prepared by an alternative method described below, melted at 97–99°.

The 1.09 g. of gelatinous-appearing material from separatory funnels no. 42–45 yielded 0.663 g. of a yellow oil after sublimation at 100° (0.01 mm.). The oil was dissolved in ether, and the solution was treated with a stream of ketene for one hour. The solid product yielded a powdery white solid, m.p. 209–210°, after a recrystallization from aqueous ethanol. A mixture of this solid with the diacetyl derivative of the diphenylene III showed no m.p. depression; but a mixture with the diacetyl derivative, m.p. 209.5–211°, of the 2,2'-diaminobiphenyl IV, gave a 30° m.p. depression. Thus the 0.663 g. of oil must have consisted largely of the diphenylene III, and the total yield of this compound is reported as 2.473 g. (9.78%).

Of the 5.99 g. of crude mixed bases which remained after the 3,5-difluoroaniline had been removed by steam distillation, 4.743 g. was accounted for as rearrangement products II, III and IV. The remaining material was substantially involatile at 0.01 mm., was difficultly soluble in ether, and softened over a wide temperature range.

2,4-Difluoro-6-nitroiodobenzene.—A nitrosylsulfuric acid solution was prepared by treating 60 ml. of concentrated sulfuric acid with 11 g. of powdered sodium nitrite, warming the mixture until complete solution occurred, and then cooling to 15°. This solution was added to another made by dissolving 27 g. of 2,4-difluoro-6-nitroaniline (VIII) in 60 ml. of concentrated sulfuric acid and cooling to 20°. The diazonium solution was maintained at 15–20° while 100 ml. of 85% phosphoric acid was added gradually. After excess nitrous acid was destroyed by treatment with 10 g. of urea in aqueous solution, the cold diazonium solution was poured into a vigorously stirred solution of 46 g. of potassium iodide in 145 ml. of water. Excess iodine was destroyed by treatment with solid sodium thiosulfate, and the dark liquid product was extracted into ether. The ether solution was washed with two portions of aqueous sodium thiosulfate, with four portions of 5% aqueous sodium hydroxide, once with 5% aqueous hydrochloric acid and once with water; then it was dried over sodium sulfate. Distillation of the crude product after removal of the ether

yielded 32.7 g. (75%) of an orange-yellow liquid, b.p. 107–108° (5 mm.). This liquid yielded small, bright yellow needles when its ethanol solution was chilled in an ice-salt-bath. Three recrystallizations carried out in the same manner gave a product of m.p. 27°.

Anal. Calcd. for $C_8H_2NO_2F_2$: C, 25.28; H, 0.70. Found: C, 25.49; H, 0.78.

4,4',6,6'-Tetrafluoro-2,2'-dinitrobiphenyl.—A mixture of 30 g. of 2,5-difluoro-6-nitroiodobenzene and 30 g. of copper powder (O. B. Hommel Co., No. 1 Extra Fine, No. 5743) was heated to 115°, when the temperature rose suddenly to 260° and then declined. The cooled mixture was extracted with boiling acetone, which was then replaced with ethanol. The hot solution was treated with two portions of decolorizing charcoal, and then the bright yellow solution when cooled yielded 10.0 g. of a yellow solid, m.p. 72–77°. Another 2.5 g. of the same compound (75% total yield) separated when the mother liquors were concentrated. Recrystallization from ethanol gave bright yellow plates, m.p. 78.5–80°.

Anal. Calcd. for $C_{12}H_4N_2O_2F_4$: C, 45.59; H, 1.26. Found: C, 45.58; H, 1.43.

2,2'-Diamino-4,4',6,6'-tetrafluorobiphenyl (IV).—A solution of 7.2 g. of 4,4',6,6'-tetrafluoro-2,2'-dinitrobiphenyl in hot ethanol was treated with 2 g. of Raney nickel and then with hydrogen under three atmospheres pressure at room temperature. The filtered solution was treated with three portions of decolorizing charcoal. Dilution of the solution with water caused the separation of 5.8 g. (~100%) of pale pink needles, m.p. 92–94°. This substance was converted after two recrystallizations from ethanol into tiny needles, m.p. 100–101°.

Anal. Calcd. for $C_{12}H_8N_2F_4$: C, 56.27; H, 3.12. Found: C, 56.30; H, 3.10.

The *N,N'*-diacetyl derivative was prepared in 83% yield by treating an ether solution of IV with ketene until precipitation of the white solid derivative, m.p. 209.5–211°, was complete. Recrystallization from aqueous ethanol gave tiny white needles of the same m.p.

Anal. Calcd. for $C_{16}H_{12}N_2O_2F_4$: C, 56.47; H, 3.56. Found: C, 56.61; H, 3.63.

The *N,N'*-bis-salicylal derivative was obtained by boiling a solution of 0.2 g. of IV with 3 ml. of salicylaldehyde for 15 minutes. The hot solution was treated with 8 ml. of ethanol and then with water until a faint cloudiness appeared. Cooling caused the separation from the solution of 0.3 g. (83%) of yellow crystals, m.p. 181–184°. The derivative formed bright yellow needles, m.p. 183–184°, after two recrystallizations from benzene-petroleum ether (b.p. 30–60°).

Anal. Calcd. for $C_{26}H_{16}N_2O_2F_4$: C, 67.24; H, 3.48. Found: C, 67.03; H, 3.58.

1,3,10,12-Tetrafluoro-6,7-diphenyldibenzo[e.g.][1,4]-diazocine (VII).—A mixture of 5.16 g. of IV and 0.420 g. of benzil was heated for 30 minutes at 160–180°; then it was dissolved in glacial acetic acid and the solution was boiled. Cooling the solution caused the separation of black prisms, m.p. 197–198°, which were converted into bright yellow prisms, m.p. 199–200°, after four recrystallizations from ethanol.

Anal. Calcd. for $C_{26}H_{14}N_2F_4$: C, 72.56; H, 3.26; N, 6.51; mol. wt., 430.4. Found: C, 72.68; H, 3.46; N, 6.29; mol. wt. (Rast), 420.

The ultraviolet absorption spectrum showed a single broad band with its maximum at 262–264 $m\mu$ ($\log \epsilon$ 4.46); this spectrum resembles that of benzil,¹¹ but not that of IV.

2,2'-Diaminobiphenyl, m.p. 78.5°, was prepared for spectroscopic examination by reducing³ 2,2'-dinitrobiphenyl which, in turn, was obtained by the Ullmann coupling of *o*-iodonitrobenzene. This coupling was effected in 61% yield by heating 20 g. of *o*-iodonitrobenzene, 20 g. of copper powder and 40 g. of clean sand to 130°. At this point the temperature of the mixture rose to 210° and then dropped. The cooled mixture was extracted with boiling benzene, the benzene solution was concentrated and diluted with petroleum ether (b.p. 65–110°), and the solution was cooled. The product separated in bright yellow flakes, m.p. 124–125°. The reported¹² m.p. is 124°.

Treatment of Hydrazobenzene with 2:1 Sulfuric Acid.—The same general procedure was applied to the reaction of hydrazobenzene with 2:1 sulfuric acid at 85–90° as had been applied to the tetrafluoro analog. The medium-insoluble solids yielded, by the same procedures, azobenzene and ben-zidine. The product solution, again by use of parallel procedures, yielded acetanilide and a residue from the steam distillation of the aniline which was extracted with ether. The ether solution was treated with acetic anhydride, and *N,N'*-diacetyldiphenylamine was obtained by removing the ether and pouring the residue into water. All products were identified by their melting points. Yields of products were reported in the Discussion section.

Ultraviolet absorption spectra were determined in 95% ethanol¹³ solution by means of a Beckman quartz spectrophotometer, Model DU.

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(13) Stock 95% ethanol found to be indistinguishable in the spectrophotometer from ethanol purified by the method of P. A. Leighton, R. W. Crary and L. T. Schipp, *THIS JOURNAL*, **63**, 3017 (1931).

[CONTRIBUTION FROM EATON LABORATORIES, DIVISION OF THE NORWICH PHARMACAL COMPANY]

Chemotherapeutic Nitrofurans. I. Some Derivatives of 3-Amino-2-oxazolidone¹

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A number of 3-amino-2-oxazolidones have been prepared by the cyclization of 2-(2-hydroxyalkyl)-semicarbazides with hydrochloric acid, the condensation of β -hydrazino alcohols with some carbonic acid esters and chlorides and the catalytic or electrolytic reduction of 3-nitro-2-oxazolidones. These 3-amino-2-oxazolidone have been converted to chemotherapeutically active 5-nitro-2-acylfuran derivatives.

During the investigation of the preparation of substituted semicarbazides² it became of interest to prepare 2-(2-hydroxypropyl)-semicarbazide. An aqueous solution of 1-hydrazino-2-propanol hydrochloride was treated with potassium cyanate and after cyanation was deemed complete the solution

was acidified. Treatment of this aqueous solution with 5-nitro-2-furaldehyde gave the expected 5-nitro-2-furaldehyde 2-(2-hydroxypropyl)-semicarbazone. In an attempt to isolate 2-(2-hydroxypropyl)-semicarbazide hydrochloride, part of the original cyanation solution was concentrated *in vacuo*, leaving a gummy residue. Since no crystalline solid was obtained, the residue was taken up in water and treated with 5-nitro-2-furaldehyde.

(1) Part of the material in this paper is the subject of U. S. Patent 2,652,402, Sept. 15, 1953 (C. A., **48**, 12179d (1954)).

(2) G. Gever and K. Hayes, *J. Org. Chem.*, **14**, 813 (1949).