[CONTRIBUTION FROM THE FULMER CHEMICAL LABORATORY, THE STATE COLLEGE OF WASHINGTON]

Preparation of Some Aminotrifluoromethyldiphenyl Sulfones as Possible Antibacterial Agents[1]

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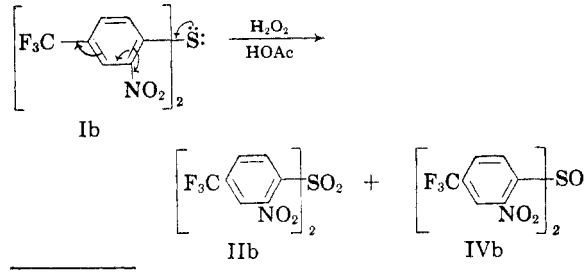
The preparation of six aminotrifluoromethyldiphenyl sulfones by way of the corresponding intermediate nitro sulfones and sulfides is described. An observation concerning the relative ease of oxidation of nitrotrifluoromethyldiphenyl sulfides to their corresponding sulfones is discussed. Of the six aminotrifluoromethyldiphenyl sulfones submitted for chemotherapy screening only the 4,4′-diamino-2-trifluoromethyldiphenyl sulfone (IIIc) showed appreciable antibacterial activity (*vs. Streptococcus pyogenes*). These results are in agreement with the principle previously established by others that amino groups in diphenyl sulfones must be situated in both *para*- positions for appreciable activity.

In previous studies by others[5] on the correlation of the structure of diaminodiphenyl sulfones with antibacterial activity, appreciable activity had been found primarily in those cases where the phenyl groups carried amino substituents in both *para*- positions. Further nuclear substitution of other groups seemed to minimize activity. We wished to study this correlation further in an additional series of substituted amino- and diaminodiphenyl sulfones, for any marked contradication to the established pattern obviously would be of interest. The trifluoromethyl group[6] was selected as the substituent to be incorporated into the present series because of interest in fluorine-substituted compounds in medicinal chemistry.[7]

The preparation of the various aminotrifluoromethyldiphenyl sulfones (Table III), which were of interest in the present study, was accomplished by the well known approach involving the corresponding nitro sulfides (Table I) and nitro sulfones (Table II) as intermediates. The unsymmetrical sulfides (Ic,d,e,f) were formed readily by the reaction of the appropriate chloronitrobenzotrifluoride with sodium *p*-nitrothiophenolate or sodium thiophenolate. The usual procedure for obtaining symmetrical sulfides such as Ia,b involves the reaction of an activated aryl halide with sodium sulfide.[6,8] A less well known procedure, which has shown promise of being superior to the sodium sulfide method, utilizes potassium ethyl xanthate as the source of the sulfide sulfur atom.[9] This method has been employed in the present work for the synthesis of symmetrical sulfides. Excellent results were obtained particularly in the case of the sulfide Ib where the yield of recrystallized product was 79%. Of comparative interest was the fact that the sulfide Ia was obtained in a crude yield of 69% (recrystallized product, 60%), wherein Caldwell and Sayin had obtained a 49% crude yield by the sodium sulfide method.[6]

In four cases, the hydrogen peroxide oxidation of nitrotrifluoromethyldiphenyl sulfides to the corresponding sulfones, either in glacial acetic acid or glacial acetic acid–acetic anhydride as solvent, gave excellent yields (85% to quantitative). However, in the case of the sulfide Ib, the corresponding sulfone IIb was obtained in a yield of only 23%. From the crude product, there also was isolated a small amount of the corresponding sulfoxide IVb (13%).



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(2) Abstracted in part from a thesis submitted by C. Richard Bresson in partial fulfillment of the requirements for the degree of Master of Science, the State College of Washington, February 1955.

(3) A portion of this work was carried out by Robert E. Harmon as an undergraduate research project, Senior in Chemistry, 1953–54.

(4) Abstracted in part from a thesis submitted by Richard C. Thamm, in partial fulfillment of the requirements for the degree of Bachelor of Science with Distinction, February, 1953.

(5) (a) Roblin, Williams, and Anderson, *J. Am. Chem. Soc.*, **63**, 1930 (1941); (b) Baker, Kadish, and Querry, *J. Org. Chem.*, **15**, 400 (1950).

(6) After this project had been initiated, Caldwell and Sayin, *J. Am. Chem. Soc.*, **73**, 5125 (1951), reported trifluoromethyl derivatives of *p*-aminobenzoic acid, sulfanilamide, and, of pertinent interest to the present subject, *p,p′*-diaminodiphenyl sulfone.

(7) A few representative references in respect to this point are: (a) Snyder, Freier, Kovacic, and Van Heyningen, *J. Am. Chem. Soc.*, 69, 371 (1947); (b) Lindenstruth and Vander Werf, *J. Am. Chem. Soc.*, **73**, 4209 (1951); (c) Hauptschein, Nodiff, and Saggiomo, *J. Am. Chem. Soc.*, 76, 1051 (1954).

(8) Connor in Gilman, ed., *Organic Chemistry*, 2nd ed., John Wiley and Sons, New York, N. Y., 1943, Vol. I, p. 855.

(9) Price and Stacy, *Org. Syntheses*, Coll. Vol. III, 667 (1955).

TABLE I
NITROTRIFLUOROMETHYLDIPHENYL SULFIDES

Sulfide	Yield, %[a]	Recryst. Solvent[b]	M.p., °C.[c]	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Sulfur, % Calcd.	Sulfur, % Found
bis-(4-Nitro-2-trifluoromethylphenyl) (Ia)	60	A	136–137[d]	$C_{14}H_6F_6N_2O_4S$						
bis-(2-Nitro-4-trifluoromethylphenyl) (Ib)	79[e]	A	144–145	$C_{14}H_6F_6N_2O_4S$	40.77	40.57	1.47	1.43	6.80	6.86
4,4′-Dinitro-2-trifluoromethyldiphenyl (Ic)	55	A	162.5–163.5	$C_{13}H_7F_3N_2O_4S$[f]	45.35	45.37	2.05	1.97	9.31	9.43
2,4′-Dinitro-4-trifluoromethyldiphenyl (Id)	38[e]	E	129–130	$C_{13}H_7F_3N_2O_4S$	45.35	45.39	2.05	2.15	9.31	9.49
4-Nitro-2-trifluoromethyldiphenyl (Ie)	81		Sirup	$C_{13}H_8F_3NO_2S$						
2-Nitro-4-trifluoromethyldiphenyl (If)	68[e]	E	72.5–73.5[g]	$C_{13}H_8F_3NO_2S$	52.15	52.20	2.76	2.81	10.73	10.56

[a] Yields reported in all Tables are those of the recrystallized products. [b] Analytical samples were recrystallized several times in each instance (all Tables). Solvents employed: A, glacial acetic acid; E, 95% ethanol. [c] M.p. of analytical sample (all Tables). All of these sulfides had the appearance of bright yellow needles or platelets. [d] Caldwell and Sayin (ref. 6) reported m.p. 136–137°. [e] 4-Chloro-3-nitrobenzotrifluoride (ref. 13) was used in the preparation of these sulfides. [f] N calcd. 8.14; found 8.15. [g] Bunnett and Davis, *J. Am. Chem. Soc.*, **76**, 3011 (1954), reported m.p. 71–72°.

TABLE II
NITROTRIFLUOROMETHYLDIPHENYL SULFONES

Sulfone	Yield,[a] %	M.p., °C.	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Sulfur, % Calcd.	Sulfur, % Found
bis-(4-Nitro-2-trifluoromethylphenyl) (IIa)	86A, 94B[b]	172–173[c]	$C_{14}H_6F_6N_2O_6S$						
bis-(2-Nitro-4-trifluoromethylphenyl) (IIb)	23B, 66C	168–168.5	$C_{14}H_6F_6N_2O_6S$	37.85	37.69	1.36	1.34	7.22	7.07
4,4′-Dinitro-2-trifluoromethyldiphenyl (IIc)	98A	193–194	$C_{13}H_7F_3N_2O_6S$	41.49	41.27	1.88	1.81	8.52	8.37
2,4′-Dinitro-4-trifluoromethyldiphenyl (IId)	41A, 74C	174–174.5	$C_{13}H_7F_3N_2O_6S$	41.49	41.57	1.88	1.82	8.52	8.69
4-Nitro-2-trifluoromethyldiphenyl (IIe)	84B[b]	159–160	$C_{13}H_8F_3NO_4S$	47.12	47.03	2.45	2.53	9.69	9.58
2-Nitro-4-fluoromethyldiphenyl (IIf)	85B[b]	148–149	$C_{13}H_8F_3NO_4S$	47.12	46.99	2.45	2.48	9.69	9.80

[a] Capital letters denote procedure used for the preparation of the sulfone. [b] Recrystallized from 85% acetic acid. The other sulfones were recrystallized from glacial acetic acid. All of the nitro sulfones had the appearance of fine, colorless needles. [c] Caldwell and Sayin (ref. 6) reported m.p. 172–173°.

TABLE III
AMINOTRIFLUOROMETHYLDIPHENYL SULFONES

Sulfone	Yield, %	M.p., °C.	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Funod	Sulfur, % Calcd.	Sulfur, % Found
bis-(4-Amino-2-trifluoromethylphenyl) (IIIa)	88[a]	210–211[b]	$C_{14}H_{10}F_6N_2O_2S$						
bis-(2-Amino-4-trifluoromethylphenyl) (IIIb)	45[c]	139–139.5	$C_{14}H_{10}F_6N_2O_2S$	43.75	43.75	2.62	2.62	8.34	8.15
4,4′-Diamino-2-trifluoromethyldiphenyl (IIIc)	95[d]	193.5–194.5[e]	$C_{13}H_{11}F_3N_2O_2S$	49.36	49.13	3.51	3.70	10.14	10.28
2,4′-Diamino-4-trifluoromethyldiphenyl (IIId)	65[f]	197–198	$C_{13}H_{11}F_3N_2O_2S$	49.36	49.46	3.51	3.64	10.14	10.02
4-Amino-2-trifluoromethyldiphenyl (IIIe)	71[g]	186.5–187.5	$C_{13}H_{10}F_3NO_2S$	51.82	51.59	3.35	3.35	10.64	10.40
2-Amino-4-trifluoromethyldiphenyl (IIIf)	73[h]	141–141.5	$C_{13}H_{10}F_3NO_2S$	51.82	51.77	3.35	3.39	10.64	10.42

[a] Purified by precipitating from 15% hydrochloric acid with 30% potassium hydroxide solution. All amino sulfones had the appearance of colorless needles or platelets. [b] Reported melting point 211–212° (ref. 6); melts with decomposition. [c] Recrystallized from 85% acetic acid. [d] Recrystallized from 80% ethanol in which was dissolved 0.01 g. of sodium hydrosulfite as an antioxidant to prevent discoloration through oxidation. [e] In a mixed melting point determination with the starting material (m.p. 193–194°, IIc, Table II), a considerable depression was observed (m.p. 160–165°). [f] Recrystallized from 60% ethanol. [g] Purified by precipitating from hot 30% hydrochloric acid solution with cold water. A residual insoluble oil was taken up in 60% ethanol, precipitated with water, filtered, dried, and treated again with hot 30% hydrochloric acid. This procedure brought about solution and purification of most of the crude product. [h] Recrystallized from 65% ethanol.

It was of interest to note that the sulfoxide IVb, m.p. 167–167.5°, had almost identically the same melting point as the sulfone IIb, m.p. 168–168.5°. Admixture of the two, however, resulted in a marked depression in melting point (132–136°).

Since the isomeric sulfide Ia underwent oxidation with hydrogen peroxide in glacial acetic acid under precisely the same conditions as the experiment with Ib to yield 94% of the pure, recrystallized sulfone IIa, the result just described relative to Ib suggested a considerably decreased tendency toward oxidation. A parallel situation in respect to oxidation also was observed for the isomeric sulfides Ic,d. Here again, the isomer with a nitro group in an *ortho-* position underwent oxidation with much greater difficulty. Difficulties in oxidizing sulfides to sulfones have been reported previously.[10] For the most part, such difficulties in oxidation were attributed to steric factors. Although undoubtedly steric hindrance in many instances would account for resistance to oxidation, in the present case it would not seem to be an important factor in explaining the results observed. Indeed, since the trifluoromethyl group is larger in size than the nitro group,[11] the direct opposite of what was observed might have been anticipated if steric hindrance was of major importance. On the other hand, the observed variations in ease of oxidation might be explained readily on the basis of electrical effects. The effect of the electron-withdrawing nitro and trifluoromethyl groups would tend to diminish the electron density on the sulfur atom for the sulfides in question (*cf.* formula Ib). To the extent that the *ortho*-nitro and *para*-trifluoromethyl combination was more effective in decreasing the sulfur electron density than in the case of the isomer, one would anticipate greater difficulty in oxidation. It is not unreasonable to conclude that this situation, indeed, obtains, for it is well known that the nitro group is a stronger electron-withdrawing group than the trifluoromethyl group and that it would be more effective in this capacity in the *ortho-* position than in the *para.*

Use of a much more vigorous oxidizing agent, chromic anhydride, expedited the preparation of the sulfones IIb,d in good yield and free of contaminating sulfoxide.

Initially, reduction of nitro sulfones to amino sulfones was attempted by means of a catalytic procedure using Raney nickel. In the case of the reduction of IIf to IIIf, the procedure was applied with good results (73% yield). But when we attempted to extend the procedure to the isomer IIe and the symmetrical sulfone IIb, we were unable to obtain the desired amino sulfones. Reduction by stannous chloride proved successful, however, and was employed, therefore, for preparation of all the other amino sulfones. Generally, the yields obtained were excellent (71–95%); however, two sulfones IIb,d gave less satisfactory yields, 45 and 65%, respectively. This result appeared to be correlated with one or both nitro groups being situated in the *ortho-* positions. Another case of the product and the starting material having virtually the same melting point was encountered in the amino sulfone series. The nitro sulfone IIc, m.p. 193–194°, was found to yield an amino sulfone IIIc with a melting point of 193.5–194.5°. Admixture of these two substances lead to a considerable depression in the melting point (160–165°).

In one run for the preparation of nitro sulfone IIa, an unexpected result was observed. A small amount of higher melting substance (206–207° *vs.* 172–173° for IIa) was isolated. Analysis confirmed its percentage composition as being that of IIa; therefore, one would conclude that it was an isomer or dimorphic form. The latter possibility appeared to be ruled out, for on reduction, the substance yielded an amino sulfone IIIa′ of higher melting point than IIIa (236–237° *vs.* 210–211°). The nature of these compounds was not investigated further.

Chemotherapy screening. None of the aminotrifluoromethyldiphenyl sulfones (Table III), with one exception, was found to be effective for mice infected with any of the following organisms: influenza virus, MM virus, *Streptococcus pyogenes,* Typhoid, *Proteus vulgaris,* or *Psuedomonas aeruginosa.* Only 4,4′-diamino-2-trifluoromethyldiphenyl sulfone (IIIc) showed appreciable antibacterial activity (*vs.* 2350 Ld_{50} in *Streptococcus pyogenes* infected mice at 10 mg. subq. × 2). Also it was interesting to note that compounds containing as much as one *ortho-* amino substituent were more toxic than those with no *ortho-* amino substituents. Thus, these results further substantiate the correlations of structure and activity observed by others.[5]

EXPERIMENTAL[12]

2-Chloro-5-nitrobenzotrifluoride. Substantially in accord with the procedure of Caldwell and Sayin,[6] 179.5 g. (1.00 mole) of *o*-chlorobenzotrifluoride[13] was added dropwise with stirring to a nitrating mixture consisting of 200.0 g. of concentrated sulfuric acid and 81.0 g. of fuming nitric acid. The temperature of the reaction mixture was maintained at 30–35° by controlling the addition of the reactant and cooling the mixture in an ice bath. After addition was complete, stirring of the mixture was continued for 30 min. at room temperature and then at 60° (water-bath). When the mixture had cooled to room temperature, the lower phase of spent acid was removed, and the crude organic

(10) (a) Baker, Querry, and Kadish, *J. Org. Chem.,* **15,** 402 (1950); (b) Horner and Medem, *Chem. Ber.,* **85,** 520 (1952); (c) Blanksma, *Rec. trav. chim.,* **20,** 425 (1901).

(11) From Fischer-Taylor-Hirschfelder models, the interference radii of the trifluoromethyl and nitro groups were determined as being 2.50 Å. and 2.35 Å., respectively.

(12) All melting points are corrected, and boiling points are uncorrected. The microanalytical work was performed by Galbraith Laboratories, Knoxville, Tenn.

(13) Obtained from Halogen Chemicals, Inc., Columbia 3, S. C.

material was washed successively with two 150-ml. portions of water, three 100-ml. portions of 2% sodium carbonate solution, and finally again with two 100-ml. portions of water. After drying over anhydrous magnesium sulfate, the product was distilled under reduced pressure; yield, 183.0 g. (81%), b.p. 64–66° (2–3 mm.), n_D^{25} 1.5058. Since the boiling point seemed somewhat lower than might have been anticipated from those previously reported,[14] a sample was submitted for analysis.

Anal. Calcd. for $C_7H_3ClF_3NO_2$: C, 37.27; H, 1.34; N, 6.21. Found: C, 37.12; H, 1.21; N, 6.16.

Further, a sample was converted into the acetyl derivative of the corresponding amine, the melting point of which (m.p. 117–117.5°) was in agreement with that reported previously.[6]

Unsymmetrical sulfides. The procedure[15] employed for the preparation of the sulfide Ic (Table I) exemplifies that used for the synthesis of unsymmetrical sulfides. To a solution of 19.3 g. (0.12 mole) of *p*-nitrothiophenol[16] in 120 ml. of absolute ethanol was added 2.85 g. (0.12 gram atom) of sodium in small pieces. To this then was added dropwise with stirring a solution of 28.0 g. (0.12 mole) of 2-chloro-5-nitrobenzotrifluoride in 130 ml. of absolute ethanol. The reaction mixture was heated under reflux for 90 min. and was cooled overnight and filtered. The product was washed with 200 ml. of hot water and dried; yield 27.7 g. (65%), m.p. 149–151°.

Symmetrical sulfides. These were prepared by the xanthate method,[9] and the details for the preparation for the sulfide Ia are illustrative. To a solution of 48.3 g. (0.30 mole) of potassium ethyl xanthate in 200 ml. of 95% ethanol was added 67.7 g. (0.30 mole) of 2-chloro-5-nitrobenzotrifluoride, and the mixture was heated under reflux for 24 hr. The reaction mixture then was diluted with 100 ml. of water and cooled. The resulting precipitate was removed by filtration and washed with hot water and cold ethanol; yield, 42.4 g. (68%), m.p. 128–131°.

Nitro sulfoxides and sulfones. Procedure A. Hydrogen peroxide oxidation in glacial acetic acid–acetic anhydride. The procedure[17] as specifically applied to conversion of the sulfide Ia to the corresponding sulfone IIa is presented. A mixture of 3.90 g. (9 mmoles) of the sulfide Ia and 45 ml. of an 8:1 glacial acetic acid–acetic anhydride solution was heated to 85–90°. After solution had occurred, 5 ml. (*ca.* 0.045 mole) of 30% hydrogen peroxide was added dropwise, and then the solution was heated under reflux for 1 hr. The fine, colorless needles were removed by filtration, washed with cold 85% acetic acid, and dried (Table II).

In one run involving the preparation of IIa from 32.4 g. (0.078 mole) of Ia by this method, an unusual result was observed. In crystallizing from the reaction mixture, the product separated into two fractions: A, 6.11 g., m.p. 191.5–192.5° and B, 21.6 g., m.p. 166–169°. Fraction B was IIa, but recrystallization of A gave a substance of considerably higher melting point (m.p. 206–207°). Although the nature of this compound has not been fully determined, analysis suggested it to be an *isomer of IIa (IIa')*.

Anal. Calcd. for $C_{14}H_6F_6N_2O_6S$: C, 37.85; H, 1.36; S, 7.22. Found: C, 38.02; H, 1.28; S, 7.10.

Procedure B. Hydrogen peroxide oxidation in glacial acetic acid. Although this procedure was employed in the oxidation of several sulfides to sulfones, its application to bis-(2-nitro-4-trifluoromethylphenyl) sulfide (Ib → IIb) is presented because of its particular interest. To 10.0 g. (0.023 mole) of Ib dissolved in 100 ml. of glacial acetic acid, which had been heated to 90°, was added dropwise 14 ml. of 30% hydrogen peroxide with stirring. The temperature was maintained at 90° for 2 hr., and then the mixture was heated under reflux for 1 hr. Finally an additional 8 ml. of hydrogen peroxide was added, and refluxing was continued for 1 hr. The mixture was allowed to cool overnight, and the yellow crystalline precipitate was removed by filtration; yield, 4.68 g., m.p. 142–145°. The filtrate was concentrated and yielded an additional 1.60 g., m.p. 128–132°. These two substances were subjected to fractional crystallization from glacial acetic acid and water (concentration adjusted by addition of small portions). There were obtained 3.45 g. (23%) of colorless needles (m.p. 168–168.5°), which was the sulfone IIb (compare with the material obtained by *Procedure C* below), and 1.33 g. (13%) of yellow platelets (m.p. 167–167.5°). This latter substance was *bis-(2-nitro-4-trifluoromethylphenyl) sulfoxide (IVb)*.

Anal. Calcd. for $C_{14}H_6F_6N_2O_5S$: C, 39.24; H, 1.43; N, 6.54. Found: C, 39.29; H, 1.42; N, 6.49.

Admixture of the pure sulfone and sulfoxide resulted in a sharply depressed melting point (132–136°).

2,4'-Dinitro-4-trifluoromethyl sulfoxide. When *Procedure A* was applied to 13.0 g. (0.038 mole) of the sulfide Id, only partial oxidation to the sulfone IId took place. There was obtained initially 11.0 g. (78%) of yellow needles, m.p. 164–167°. Fractional recrystallization of this product gave 5.80 g. (41%) of sulfone, m.p. 174–174.5°, and 1.60 g. (11%) of the corresponding sulfoxide, m.p. 134.5–135°.

Anal. Calcd. for $C_{13}H_7F_3N_2O_5S$: C, 43.34; H, 1.96; S, 8.90. Found: C, 43.54; H, 1.96; S, 9.10.

Procedure C. Chromic anhydride oxidation. This method[18] is briefly outlined as applied to the preparation of the sulfone IIb. To 2.72 g. (6.6 mmoles) of Ib dissolved in 30 ml. of glacial acetic acid was added 2.00 g. (20 mmoles) of chromic anhydride, as the mixture was being heated under reflux. Heating under reflux was continued for 12 hr., and the reaction mixture then was cooled and poured into water; the greenish white precipitate was removed by filtration and washed with water. When this product was admixed with the sulfone obtained in *Procedure B* above, no depression of melting point was observed.

Amino sulfones. One nitro sulfone was reduced catalytically by the procedure of Gilman and Broadbent.[15] However, the procedure,[19] which was employed in the reduction of all but one of the nitro sulfones, is illustrated as follows by the preparation of bis-(2-amino-4-trifluoromethylphenyl) sulfone (IIIb) (Table III). Anhydrous hydrogen chloride (generated according to Maxson[20]) was introduced into a mixture of 50.0 g. (0.22 mole) of stannous chloride dihydrate, 50 ml. of glacial acetic acid, and 5 ml. of water until the solution became saturated; during this period the mixture was stirred and heated to 80°. Then 9.30 g. (0.022 mole) of the nitro sulfone IIb was added, and when the vigorous reaction had subsided, the solution was heated to 80° for 2 hr. Then the solution was poured into 200 ml. of water and cooled, and the colorless product was removed by filtration and washed with 30% potassium hydroxide solution followed by water.

It was observed that reduction of the nitro sulfones at 80° or above always lead to a considerable amount of color in the product which was difficult to remove. Finally, it was observed (for IIIa and IIId) that discoloration was avoided and that the yields were improved if the reaction temperature was maintained below 55° during the first half hour.

Aminotrifluoromethyldiphenyl sulfone isomer (IIIa'). The

(14) Caldwell and Sayin (ref. 6) reported b.p. 108° (10 mm.), and a French patent reported 102–103° (5 mm.), *Chem. Abstr.*, **27**, 4414 (1933).

(15) Gilman and Broadbent, *J. Am. Chem. Soc.*, **69**, 2053 (1947).

(16) Price and Stacy, *J. Am. Chem. Soc.*, **68**, 498 (1946).

(17) Burton and Hoggarth, *J. Chem. Soc.*, 468 (1945).

(18) Shriner, Struck, and Jorison, *J. Am. Chem. Soc.*, **52**, 2060 (1930).

(19) (a) Price, Leonard, and Stacy, *J. Am. Chem. Soc.*, **69**, 855 (1947); (b) Amstutz, *J. Am. Chem. Soc.*, **72**, 3420 (1950).

(20) Maxson in Booth, Ed., *Inorganic Syntheses*, McGraw-Hill, New York, N. Y., 1939, Vol. I, p. 147.

nitrotrifluoromethyldiphenyl sulfone isomer (IIa'), which had been isolated in the process of the preparation of sulfone IIa, was subjected to reduction by the stannous chloride procedure. From 500 mg. (1.1 mmoles) of IIa' there was obtained 290 mg. (67%) of yellow, granular crystals, m.p. 236–237°.

Anal. Calcd. for $C_{14}H_{10}F_6N_2O_2S$: C, 43.75; H, 2.62; S 8.34. Found: C, 43.78; H, 2.62; S, 8.59.

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PULLMAN, WASH.

[CONTRIBUTION FROM THE DEPARTMENT OF ORGANIC CHEMISTRY, RADIUM INSTITUTE, UNIVERSITY OF PARIS]

1,2,2-Triarylethylenes Substituted with Higher Alkyl Groups

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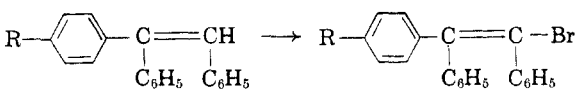
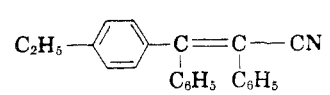
A number of 1-bromo- and 1-cyano-1,2,2-triarylethylenes, bearing higher alkyl groups, and possessing only a weak estrogenic activity, have been synthesized for biological investigation as potential chemical inhibitors of the anterior pituitary secretions.

1,2,-Triarylethylenes, especially those bearing a halogen or a cyano substituent in the ethylene bridge, form a biologically interesting group comprising several substances of remarkably high estrogenic potency (as for instance, 1-bromo- and 1-cyano-1,2,2-triphenylethylene,[1] 1-bromo-1-phenyl-2,2-di(4-ethoxyphenyl)ethylene, 1-chloro-1,2,2-trianisylethylene,[2] etc.) These estrogenic 1,2,2-triarylethylenes are also chemical inhibitors of the secretions of the anterior pituitary,[3] especially of the somatotrophic hormone, and some have found practical use in the chemotherapy of cancer[4]; in this series, the estrogenic activity is known to decrease sharply with the introduction of alkyl substituents in *para-* positions.[1] Now, it has recently been found that some 1,2,-triarylethylenes bearing higher alkyl groups, such as 1-bromo-1,2-diphenyl-2-(4-*n*-butylphenyl)ethylene (III), are good inhibitors of growth in mice, while displaying only a negligible estrogenic activity[5]; compound III inhibits also the effect of gonadotrophin on the ovaries in female mice, but has little action on the development of the testicles in male animals. These observations led us to synthesize, for biological evaluation in this domain, a number of homologs and analogs of compound (III) bearing higher alkyl groups or other bulky substituents in the benzene rings.

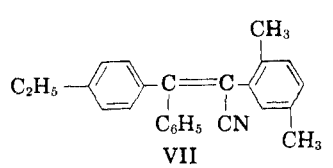


I; R = *n*-C_5H_{11}
II; R = *n*-C_6H_{13}
III; R = *n*-C_4H_9
IV; R = *n*-C_5H_{11}
V; R = *n*-C_6H_{13}

The reaction of benzylmagnesium chloride on 4-*n*-amyl- and 4-*n*-hexylbenzophenone yielded tertiary alcohols which were directly dehydrated with formic acid to 1,2-diphenyl-2-(4-*n*-amylphenyl)- (I) and 1,2-diphenyl-2-(4-*n*-hexylphenyl)ethylene (II), respectively; these liquid hydrocarbons readily underwent bromination to give 1-bromo-1,2-diphenyl-2-(4-*n*-amylphenyl)- (IV) and 1-bromo-1,2-diphenyl-2-(4-*n*-hexylphenyl)ethylene (V), both of which were well crystallized compounds. In these bromination reactions, it was observed that only one of the two possible stereoisomeric ethylenes was formed; on the other hand, the sodium amide–catalyzed condensation of 4-ethylbenzophenone with benzyl cyanide[6] yielded 1,2-diphenyl-2-(4-ethylphenyl)acrylonitrile (VI) in both stereoisomeric forms.



VI



VII

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