Anal. Calcd. for $C_{21}H_{29}NO_3\cdot HClO_4$: C, 56.82; H, 6.81. Found: C, 56.98; H, 6.55.

Acknowledgment.—The authors are indebted to Mr. R. N. Boos and his staff for the microanalyses reported in this paper. In addition we wish to record our sincere appreciation for the pharmacological work carried out by Drs. C. A. Winter and P. D. Orahovats and their associates L. Flataker and E. L. Lehman of the Merck Institute for Therapeutic Research.

RAHWAY, NEW JERSEY

[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF THE SPRAGUE ELECTRIC CO.]

Tetrakis-(trifluoromethyl)-biphenyls

BY SIDNEY D. ROSS, MOUSHY MARKARIAN AND MEYER SCHWARZ

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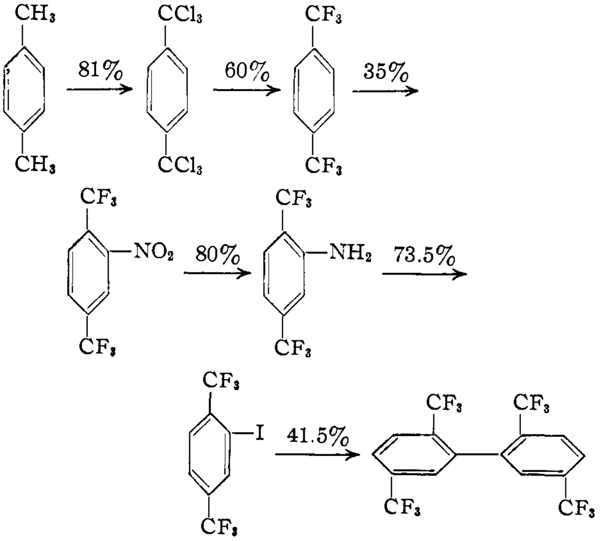
2,2′,5,5′-Tetrakis-(trifluoromethyl)-biphenyl and 3,3′,5,5′-tetrakis-(trifluoromethyl)-biphenyl have been synthesized, and their ultraviolet absorption spectra have been determined.

For applications requiring a dielectric constant in excess of four, the dielectrics most commonly used are the chlorinated biphenyls and naphthalenes. These materials are of limited stability in an electric field, particularly at elevated temperatures. In most respects, trifluoromethyl groups are desirable replacements for the chlorine groups. They have a relatively large dipole moment,[1] and are very stable chemically, except when ortho or para to a strongly ortho–para directing group.[2]

The only trifluoromethyl substituted biphenyls which have been prepared and characterized are the 3-trifluoromethylbiphenyl,[3] 3,3′-bis-(trifluoromethyl)-biphenyl,[3,4] and 4,4′-bis-(trifluoromethyl)-biphenyl.[4,5] Since the trifluoromethyl group has a large positive σ-constant,[1] an iodobenzene containing two trifluoromethyl groups should undergo the Ullmann reaction. We have taken advantage of this consideration to prepare 3,3′,4,4′-tetrakis-(trifluoromethyl)-benzene and 2,2′,5,5′-tetrakis-(trifluoromethyl)-benzene. The reaction sequence shown below was used to prepare the latter compound and a completely similar reaction sequence resulted in the former.



The ultraviolet absorption spectra of the two tetrakis-(trifluoromethyl)-biphenyls are of interest. These are presented in Fig. 1, in which the spectra of benzotrifluoride, 1,4-bis-(trifluoromethyl)-benzene and 3,3′-bis-(trifluoromethyl)-biphenyl are included for purposes of comparison.

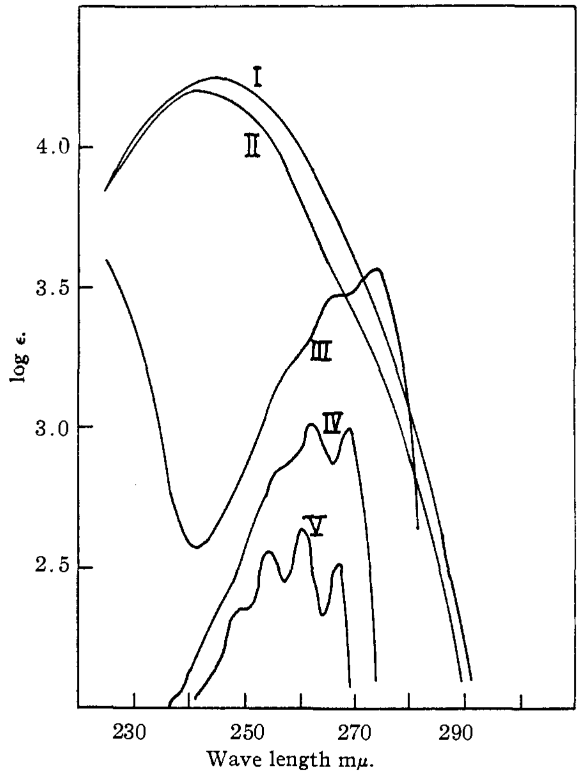


Fig. 1.—Ultraviolet absorption spectra of trifluoromethyl substituted compounds in 2,2,4-trimethylpentane: I, 3,3′-bis-(trifluoromethyl)-biphenyl; II, 3,3′,5,5′-tetrakis-(trifluoromethyl)-biphenyl; III, 2,2′,5,5′-tetrakis-(trifluoromethyl)-biphenyl; IV, 1,4-bis-(trifluoromethyl)-benzene; V, benzotrifluoride.

Benzotrifluoride (log ϵ_{max} 2.6 at 260 mμ)[6] shows

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[1] J. D. Roberts, R. L. Webb and E. A. McElhill, THIS JOURNAL, **72**, 408 (1950).

[2] R. G. Jones, *ibid.*, **69**, 2346 (1947).

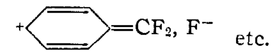
[3] C. K. Bradsher and J. B. Bond, *ibid.*, **71**, 2659 (1949).

[4] M. Markarian, *ibid.*, **74**, 1858 (1952).

[5] S. D. Ross and I. Kuntz, *ibid.*, **74**, 1297 (1952).

[6] This spectrum is in excellent agreement with that reported by C. H. Miller and H. W. Thompson for benzotrifluoride in *n*-heptane; *J. Chem. Phys.*, **17**, 845 (1949).

greater absorption than benzene (log ϵ_{max} 2.4 at 255 mμ in hexane).[7] The greater absorption indicates that structures of the type[1]



make an important contribution to the excited states. 1,4-Bis-(trifluoromethyl)-benzene (log ϵ_{max} 3.0 at 262 mμ)[8] shows more than twice the absorption of benzotrifluoride, probably because this compound can have double the number of "no-bond" structures of the above type.

Both 3,3′-bis-(trifluoromethyl)-biphenyl and 3,3′-5,5′-tetrakis-(trifluoromethyl)-biphenyl show absorption typical of biphenyl (ϵ_{max} 20,300 at 246 mμ in hexane).[9] 3,3′-Bis-(trifluoromethyl)-biphenyl shows somewhat lower absorption (ϵ_{max} 17,780 at 245 mμ) probably because any resonance interaction between the trifluoromethyl groups and the benzene rings acts as a partial barrier to the formation of the excited biphenyl structures having a double bond between the two rings. This effect is further accentuated in 3,3′,5,5′-tetrakis-(trifluoromethyl)-biphenyl (ϵ_{max} 15,850 at 242 mμ), since this compound has four trifluoromethyl groups, all so situated that interaction with the benzene rings will impose a barrier to formation of a double bond between the two rings.

In 2,2′,5,5′-tetrakis-(trifluoromethyl)-biphenyl, the 2,2′-trifluoromethyl groups are sufficient to prevent coplanarity of the two benzene rings and inhibit resonance between them.[10] The resultant spectrum is similar to that of benzotrifluoride and 1,4-bis-(trifluoromethyl)-benzene but displaced to longer wave lengths (ϵ_{max} 3,630 at 274 mμ). As a first approximation one might expect this hindered biphenyl to absorb with twice the intensity of 1,4-bis-(trifluoromethyl)-benzene on a molar basis. Actually, the observed absorption is appreciably higher than that. However, similar effects have been observed by Williamson and Rodebush[11] in the case of aniline and 2,2′-diaminobiphenyl and in the case of anisole and 2,2′-dimethoxybiphenyl.

Experimental[12]

1,4-Bis-(trichloromethyl)-benzene.[13]—The chlorination of *p*-xylene was carried out in a long tube with a fritted glass disc at the bottom for a chlorine inlet and reflux condenser at the top. The tube was wrapped with nichrome wire, and enough current was supplied to keep the reaction mixture molten throughout the chlorination. The entire apparatus was illuminated with two black light fluorescent tubes. The apparatus was charged with *p*-xylene (212 g., 2 moles), which was chlorinated to a gain in weight of 411 g. The reaction mixture was poured into an evaporating dish while still molten and, after cooling, was crystallized from hexane to yield 500 g. (81%) of 1,4-bis-(trichloromethyl)-benzene, m.p. 108–110°.

1,4-Bis-(trifluoromethyl)-benzene.[14]—1,4-Bis-(trichloromethyl)-benzene (923 g., 2.96 moles) and antimony trifluoride (1070 g., 6 moles) were ground together in a mortar and then separated into three portions. Each portion was placed in a 500-cc. flask fitted with a condenser set for distillation. The flask was heated with a bunsen flame until reaction started, and the heating was continued until no further liquid distilled. The combined distillates, 592 g., were washed with concentrated hydrochloric acid two times, water and finally 10% sodium hydroxide. The crude product was steam distilled; the organic layer was separated and dried over anhydrous magnesium sulfate. Fractionation at atmospheric pressure yielded 380 g. (60%) of the hexafluoride, b.p. 115.5–118°. In addition, there was obtained 125 g. of an unidentified liquid boiling above 118°.

2-Nitro-1,4-bis-(trifluoromethyl)-benzene.—To 1,4-bis-(trifluoromethyl)-benzene (243 g., 1.135 moles), cooled to 5–10°, in a two-liter, three-neck flask, fitted with a stirrer, thermometer, dropping funnel and reflux condenser, was added 24% fuming sulfuric acid (484 g.). Then the dropwise addition of 100% nitric acid (291 g.) was started. Initially, the reaction was very exothermic, and cooling with a Dry Ice–trichloroethylene-bath was necessary. After one-third of the nitric acid was added, it was possible to increase the drop rate. After the addition, the cooling bath was removed, and the reaction was permitted to come to room temperature. It was then heated to 90–100° for one hour. Fuming sulfuric acid (192 g.) and 100% nitric acid (134 g.) were added, and the reaction mixture was heated at 100–105° for two hours. It was then cooled and poured onto ice. The organic layer was separated, and the aqueous layer was extracted with chloroform. The product and extracts were combined, washed with water, 10% sodium hydroxide and water again. The solution was dried over anhydrous magnesium sulfate, the solvent was removed at atmospheric pressure, and the product was distilled at 11 mm. to yield 105 g. (35%) of the nitro compound, b.p. 83°. A sample redistilled for analysis had b.p. 90.5° at 15 mm. and n^{20}_D 1.4260.

Anal. Calcd. for $C_8H_3O_2NF_6$: C, 37.05; H, 1.17. Found: C, 37.08, 36.79; H, 1.00, 1.04.

2-Amino-1,4-bis-(trifluoromethyl)-benzene.—2-Nitro-1,4-bis-(trifluoromethyl)-benzene (244 g., 0.94 mole) was added to stannous chloride dihydrate (644 g.) in concentrated hydrochloric acid (857 g.). The mixture was stirred; after 1.5 hours the temperature reached 45°. The mixture was permitted to stand overnight and was then heated to 80–90° for two hours, at which time the solution became clear. It was cooled and neutralized with 700 g. of sodium hydroxide in 1.5 l. of water. The product was isolated by steam distillation, dried and distilled at 9 mm. to yield 170 g. (80%) of the amine, b.p. 63–65°. A sample redistilled for analysis had b.p. 70.5° at 14.5 mm. and n^{20}_D 1.4322.

Anal. Calcd. for $C_8H_5NF_6$: C, 41.94; H, 2.20. Found: C, 42.01, 41.74; H, 2.40, 2.58.

The acetyl derivative, prepared in the usual manner and crystallized three times from ethanol had m.p. 146.5–147°.

Anal. Calcd. for $C_{10}H_7ONF_6$: C, 44.29; H, 2.60. Found: C, 44.85, 44.69; H, 2.46, 2.56.

2-Iodo-1,4-bis-(trifluoromethyl)-benzene.—2-Amino-1,4-bis-(trifluoromethyl)-benzene (22.9 g., 0.1 mole) was added to concentrated hydrochloric (100 g.) with stirring. Chopped ice (50 g.) was added, and the reaction mixture was cooled to 0–5° with an ice-bath. A solution of sodium nitrite (7.25 g.) in water (35 cc.) was added dropwise with cooling, and this was followed by a solution of potassium iodide (16.7 g.) in water (50 cc.). Reaction was instantaneous, and an oil settled to the bottom of the flask. The mixture was permitted to stand three hours then heated from 60–70° for three hours. After cooling, the organic layer was separated, washed with water, dilute sodium hydroxide and sodium bisulfite solution. It was dried and distilled at 9 mm. to yield 25 g. (73.5%) of the iodide, b.p. 64–65°. A sample redistilled for analysis had b.p. 62° at 9 mm. and n^{20}_D 1.4693.

Anal. Calcd. for $C_8H_3F_6I$: C, 28.25; H, 0.89. Found: C, 28.34, 28.75; H, 0.64, 0.47.

2,2′,5,5′-Tetrakis-(trifluoromethyl)-biphenyl.—A mixture of 2-iodo-1,4-bis-(trifluoromethyl)-benzene (23 g., 0.068 mole), copper power (24.9 g.) and sand (23 g.) was heated

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[7] A. Hillmer and E. Paersch, *Z. physik. Chem.*, **A161**, 46, 58 (1932).

[8] This spectrum is in good agreement with that reported by C. D. Cooper and F. W. Noegel for this compound in the same solvent; *J. Chem. Phys.*, **20**, 1903 (1952).

[9] A. E. Gillam and D. H. Hey, *J. Chem. Soc.*, 1170 (1939).

[10] L. W. Pickett, G. F. Walter and H. France, THIS JOURNAL, **58**, 2296 (1936); M. Calvin, *J. Org. Chem.*, **4**, 256 (1939); M. T. O'Shaughnessy and W. H. Rodebush, THIS JOURNAL, **62**, 2906 (1940).

[11] B. Williamson and W. H. Rodebush, *ibid.*, **63**, 3018 (1941).

[12] All microanalyses are by the Laboratory of Microchemistry or the Clark Microanalytical Laboratory.

[13] C. Slesser and S. R. Schram, "Preparation, Properties and Technology of Fluorine and Organic Fluoro Compounds," McGraw-Hill Book Co., Inc., New York, N. Y., 1951, p. 815.

[14] For an alternate fluorination method see ref. 12, p. 229.

to reflux. The reflux temperature gradually rose to 220° over a period of 5–6 hours. The heating was continued an additional 8 hours. The mixture was cooled, and the product was extracted with benzene. The benzene solution was filtered and dried. The benzene was removed, and the crude product was distilled at 10 mm. to yield 6 g. (41.5%) of the biphenyl, b.p. 103–105°. On standing the product crystallized. After three crystallizations from methanol, the m.p. was 95.5–96.5°.

Anal. Calcd. for $C_{16}H_6F_{12}$: C, 45.09; H, 1.42; F, 53.50. Found: C, 45.13, 45.17; H, 1.57, 1.51; F, 53.76, 53.92.

5-Nitro-1,3-bis-(trifluoromethyl)-benzene.—The procedure was identical to that used to prepare 2-nitro-1,4-bis-(trifluoromethyl)-benzene. The starting material was 1,3-bis-(trifluoromethyl)-benzene.[15] The reaction gave 66.5% of product of b.p. 75–77° at 10 mm. A sample redistilled for analysis had b.p. 75.5° at 11 mm. and n^{25}_{D} 1.4250.

Anal. Calcd. for $C_8H_3O_2NF_6$: C, 37.05; H, 1.17. Found: C, 37.08, 36.88; H, 1.02, 1.18.

5-Amino-1,3-bis-(trifluoromethyl)-benzene.—Reduction of 5-nitro-1,3-bis-(trifluoromethyl)-benzene with stannous chloride by the procedure previously described gave an 80% yield of the amine; b.p. 75–78° at 10 mm. A sample redistilled for analysis had b.p. 75.5–76° at 10 mm. and $n^{24.5}_{\mathrm{D}}$ 1.4318.

Anal. Calcd. for $C_8H_5F_6N$: C, 41.94; H, 2.20. Found: C, 41.07, 41.20; H, 2.09, 2.17.

The acetyl derivative prepared in the usual way and recrystallized from benzene melted from 152.5–154°.[16]

Anal. Calcd. for $C_{10}H_7ONF_6$: C, 44.29; H, 2.62. Found: C, 43.56, 43.78; H, 2.51, 2.71.

5-Iodo-1,3-bis-(trifluoromethyl)-benzene.—The procedure previously described applied to 5-amino-1,3-bis-(trifluoromethyl)-benzene resulted in a 66.5% yield of the iodide, b.p. 59–61° at 10 mm., n^{25}_{D} 1.4592.

Anal. Calcd. for $C_8H_3F_6I$: C, 28.26; H, 0.89. Found: C, 28.30, 28.04; H, 1.05, 0.89.

3,3′-5,5′-Tetrakis-(trifluoromethyl)-benzene.—With the above iodide the previously described Ullmann procedure gave a 30% yield of the biphenyl of b.p. 120–124° at 10 mm. After three crystallizations from methanol the product had a m.p. of 85–86°.

Anal. Calcd. for $C_{16}H_6F_{12}$: C, 45.09; H, 1.42; F, 53.50. Found: C, 44.99, 44.84; H, 1.17, 1.28; F, 53.96; 53.01.

Ultraviolet Absorption Spectra.—A Beckman model DU quartz spectrophotometer was employed for the determinations. The solvent employed was, in all cases, Spectro Grade isoöctane (2,2,4-trimethylpentane) from the Phillips Petroleum Company.

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[15] We are indebted to the Hooker Electrochemical Company for samples of pure 1,3- and 1,4-bis-(trifluoromethyl)-benzene.

[16] N. L. Drake, *et al.*, *ibid.*, **68**, 1602 (1946). These workers nitrated a mixture of 1,3- and 1,4-bis-(trifluoromethyl)-benzene, reduced the mixed nitro compounds to the mixed amines, acetylated and finally separated the 5-acetamino-1,3-bis-(trifluoromethyl)-benzene, for which they report a melting point of 156.2–157.2°.

NORTH ADAMS, MASS.

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF CALIFORNIA]

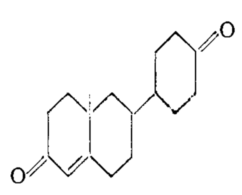
The Hydrogenation of 4-Hydroxybiphenylcarboxylic Acids

BY WILLIAM G. DAUBEN AND MASATO TANABE

RECEIVED MAY 11, 1953

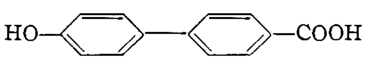
When 4-hydroxybiphenyl-4′-carboxylic acid was hexahydrogenated over Raney nickel in alkali, reaction occurred only in the hydroxyl substituted ring and both a *cis* and a *trans* isomer was isolated. Perhydrogenation yielded only one pure product which was shown to possess the *trans* configuration in the carboxyl substituted ring. When 4-hydroxybiphenyl-3′-carboxylic acid was hexahydrogenated, again reaction occurred only in the hydroxyl substituted ring but only one isomer was isolated.

In recent years, a great deal of interest has been centered about the preparation of compounds related to biologically active steroids and noticeable success has been achieved in certain series in which part of the steroid ring system has been omitted. For example, the work of Miescher and his group[1] on the bisdehydrodoisynolic acids and Horeau and Jacques[2] on the allenoic acids has indicated the extent to which the basic tetracyclic ring system can be varied and still retain biological activity. Another interesting study has been reported by Wilds[3] where it was found that compound I, lacking ring C but otherwise closely related to a homoandrosterone, possessed definite androgenic activity.

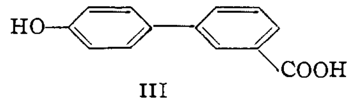


I

It is evident that the synthesis of other related steroidal model compounds could be accomplished if partially or fully hydrogenated derivatives of substituted biphenyls were available. The most useful starting materials for such a study would be the hydrogenated derivatives of 4-hydroxybiphenyl-4′-carboxylic acid (II) and its 3′-carboxylic acid isomer III. The preparation of reduced derivatives of acid II has been previously investigated. Johnson[4] has reported the preparation of one isomer, 4-(4-hydroxyphenyl)-cyclohexylcarboxylic acid (IV), by nitration of 4-phenylcyclohexylcarboxylic acid followed by reduction and diazotization or by the sodium and alcohol reduction of the methyl ether of II.[5] The isomeric hexahydro isomer V has been prepared by



II



III

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[1] G. Anner and K. Miescher, *Helv. Chim. Acta*, **30**, 1422 (1947), and earlier papers.

[2] A. Horeau and J. Jacques, *Bull. soc. chim. France*, 707 (1948), and earlier papers.

[3] A. L. Wilds and C. H. Shunk, THIS JOURNAL, **72**, 2388 (1950).

[4] W. S. Johnson and R. D. Offenhauer, *ibid.*, **67**, 1045 (1945).

[5] W. S. Johnson, G. D. Gutsche and R. D. Offenhauer, *ibid.*, **68**, 1648 (1946).