bromine and about 0.2 g. of C. P. iron powder. A weighed amount (about 1 ml.) of alkylbenzene was then added over a period of an hour. The mixture was stirred periodically, allowed to remain in the ice-bath for an additional hour, and then removed for evaporation of the excess bromine. When practically free of bromine, the residue was thoroughly washed with water and finally with sodium carbonate solution. A few products were gummy at this stage and it was found desirable to wash these with warm sodium thiosulfate solution. The samples were air-dried and purified by repeated crystallization. Hexabromobenzene and pentabromotoluene were crystallized from chlorobenzene, β-(pentabromophenyl)-ethyl bromide and γ-(pentabromophenyl)-*n*-propyl bromide from isopropyl alcohol. The other compounds were crystallized from ethyl alcohol. Use of decolorizing carbon in the second crystallization usually resulted in nearly colorless well defined crystals. Each product was prepared many times and commonly from different sources (*cf.* Table I). The yields averaged about 60% of the theoretical. Melting points were taken with a 360° thermometer calibrated against a set of fractional-degree partial immersion thermometers; the values may be considered equivalent, therefore, to corrected melting points.

Mixtures.—Synthetic mixtures, *e. g.*, *n*-propyl- with isopropylbenzene, isobutyl- with *t*-butylbenzene, etc., were brominated, washed, and dried as described above. The crude product was extracted several times with small portions of boiling 95% alcohol. Extracts were combined and concentrated by boiling to the beginning of crystallization; on cooling, the polybromoalkylbenzene deposited and was purified by repeated crystallization. The original residue was then taken up in hot chlorobenzene and the hexabromobenzene worked up in the usual manner.

Summary

1. A study has been made of the nuclear polybromination of fifty-five alkyl- and polyalkylbenzenes. Bromination with liquid bromine in the presence of iron powder at zero degrees substituted the benzene ring completely with replacement of all secondary and tertiary alkyl groups. Primary alkyl groups were not affected.

2. Mixtures of the two types of alkylbenzenes, one containing replaceable and the other nonreplaceable alkyl groups, were found to behave normally; each compound gave its own characteristic polybromo derivative.

3. Ten new polybromoalkylbenzenes are described.

NOTRE DAME, INDIANA RECEIVED NOVEMBER 29, 1945

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF IOWA STATE COLLEGE]

Some Compounds Containing the Trifluoromethyl Group

BY H. GILMAN, L. TOLMAN, F. YEOMAN, L. A. WOODS, D. A. SHIRLEY AND S. AVAKIAN

Incidental to some studies on fluorine-containing organic compounds, it appeared that certain special properties of trifluoromethyl types warranted their examination as antimalarials. Among the compounds first examined, two simple ones showed positive action in avian malaria: *m*-trifluoromethylphenol and *m*-trifluoromethylaniline. Subsequent tests showed these compounds to have a doubtful activity, and then no essential activity. Of the other compounds tested the only one with activity is *m*-trifluorophenylarsonic acid, and the specific contribution of the trifluoromethyl group to such activity is uncertain. The patent literature describes 4-(4′-diethylamino-1-methylbutylamino)-7-(trifluoromethyl)-quinoline,[1] 4-acetylamino-3′,5′-bis-(trifluoromethyl)-benzene-sulfonanilide,[2a] 4-nitro-3′,5′-bis-(trifluoromethyl)-benzenesulfonanilide[2a] and 4-amino-3′,5′-bis(trifluoromethyl)-benzenesulfonanilide.[2a] These compounds were very probably examined for antimalarial action. In addition, a mono-fluoride has been reported: 2-methoxy-6-fluoro-9-(4-diethylaminobutylamino)-acridine,[2b] and this showed no activity.

The preparation of γ-diethylaminopropyl γ-(*m*-trifluoromethylanilino)-propyl sulfide and its dihydrochloride were described recently.[3]

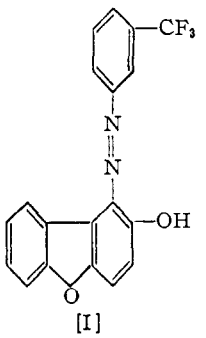
(1) Andersag, Breitner and Jung, German Patent 683,692 (1939); *C. A.*, **36**, 4973 (1942).

(2) (a) Behnisch, Klarer and Mietzsch, U. S. Patent 2,248,911 (1941); *C. A.*, **35**, 6738 (1941); (b) Magidson and Travin, *J. Gen. Chem.*, U. S. S. R., **11**, 243 (1941); *C. A.*, **35**, 7965 (1941).

(3) Gilman and Tolman, THIS JOURNAL, **67**, 1847 (1945).

Experimental

***m*-Trifluoromethylbenzenediazonium Chloride and 2-Hydroxydibenzofuran.**—The diazonium solution from 2.62 g. (0.0163 mole) of *m*-trifluoromethylaniline was added slowly and with stirring to a cold solution of 3 g. (0.0163 mole) of 2-hydroxydibenzofuran in potassium hydroxide. The temperature was kept below 5° and stirring was continued for thirty minutes. The crude coupling product was filtered and then recrystallized from glacial acetic acid to give 2.7 g. (46.5%) of fine red needles of 1-(*m*-trifluoromethylphenylazo) - 2 - hydroxydibenzofuran [I] melting at 173–174°. From a second experiment starting with 5 g. of 2-hydroxydibenzofuran, the yield was 49.7%.



[I]

Anal. Calcd. for $C_{19}H_{11}O_2N_2F_3$: N, 7.86. Found: N, 7.94.

The structure of this compound, as well as that of the one which follows, is based on the knowledge that benzenediazonium chloride couples with 2-hydroxydibenzofuran in the 1-position to give 1-phenylazo-2-hydroxydibenzofuran.[4]

***m*-Trifluoromethylbenzenediazonium Chloride and 2,8-Dihydroxydibenzofuran.**—From a diazo coupling reaction involving 8 g. (0.04 mole) of 2,8-dihydroxydibenzofuran, 6.7 g. of potassium hydroxide in 200 cc. of water and 6.42 g. (0.04 mole) of *m*-trifluoromethylaniline, 10 cc. of concentrated hydrochloric acid and 2.72 g. of sodium nitrite, a deep reddish orange product separated immediately. This was filtered and extracted several times with 50 cc. portions of boiling 5% potassium hydroxide solution until acidification of a sample of the filtrate showed that no appreciable amount of material was being extracted. The combined, dark red extracts were acidified with hyd-

(4) Gilman and Van Ess, *ibid.*, **61**, 3146 (1939).

chloric acid, and the precipitate which formed on this treatment was recrystallized from glacial acetic acid as orange-brown needles melting at 256–257°. This 1-(*m*-trifluoromethylphenylazo)-2,8-dihydroxydibenzofuran was obtained in a yield of 3 g. (20.1%). From a second preparation, the yield was 15.5%. The alkali-insoluble material was not purified.

Anal. Calcd. for $C_{19}H_{11}O_3N_2F_3$: N, 7.53. Found: N, 7.49.

m-Trifluoromethylbromobenzene.—This compound was prepared in essential accordance with the directions of Simons and Ramler.[5] The yields in two preparations, each starting with 1.82 moles of benzotrifluoride, were 54 and 55%. Two constants hitherto not reported are: $n^{20}D$ 1.4749, d^{20}_{27} 1.606.

The Grignard reagent of this *m*-trifluoromethylbromobenzene was also prepared in accordance with their directions, and used in the following experiment for the preparation of *m*-trifluoromethylbenzaldehyde by the general procedure of Smith and Bayliss.[6]

m-Trifluoromethylbenzaldehyde.—To a *m*-trifluoromethylphenylmagnesium bromide solution (prepared in ether from 45 g. or 0.2 mole of *m*-bromobenzotrifluoride and 0.2 g. atom of magnesium) cooled in an ice-bath was added 27 g. (0.2 mole) of N-methylformanilide.[7] The addition was rapid (being completed in three minutes), and color test I[8] was negative after five minutes. Stirring was continued for three hours, during which time a granular yellow precipitate separated. The cooled mixture was hydrolyzed by the careful addition of sulfuric acid; the ether layer was separated and washed with sodium bicarbonate solution, then dried over calcium chloride and distilled under reduced pressure in a nitrogen atmosphere. The yield of colorless aldehyde was 51.8%; b. p., 64–66° (10 mm.); $n^{20}D$ 1.4660; and d^{20}_{27} 1.300.

From a second preparation (of 0.4 mole size) in which the solution of *m*-trifluoromethylphenylmagnesium bromide was cooled in an ice-salt bath so that the N-methylformanilide could be added more rapidly, the yield of *m*-trifluoromethylbenzaldehyde was 59%.

m-Trifluoromethylbenzaldehyde 2,4-dinitrophenylhydrazone was prepared by refluxing an ethanolic solution of 0.5 g. (0.0029 mole) of *m*-trifluoromethylbenzaldehyde and 0.56 g. (0.0029 mole) of 2,4-dinitrophenylhydrazine. The compound crystallized as yellow needles melting at 259–260° from a mixture of ethanol, chloroform and ethyl acetate in which it is only very sparingly soluble.

Anal. Calcd. for $C_{14}H_9O_4N_4F_3$: N, 15.81. Found: N, 15.93.

N-(*m*-Trifluoromethylbenzal)-*m*-trifluoromethylaniline was prepared by refluxing for one hour a solution of 5.48 g. (0.032 mole) of *m*-trifluoromethylbenzaldehyde and 5.3 g. (0.033 mole) of *m*-trifluoromethylaniline in 50 cc. of benzene. After the benzene layer had been dried over potassium carbonate, the solution was distilled; and from the fraction distilling at 139–140° (3 mm.) was obtained 4.2 g. (42%) of a yellow oil which soon crystallized as needles melting at 49.5–51.5°. From a second preparation in which the reactants were refluxed for five hours, the yield was 62%. The products from the two runs were combined and crystallized from a very small quantity of petroleum ether (b. p., 28–38°) as colorless needles melting at 50–51°. Attempts to crystallize the N-(*m*-trifluoromethylbenzal)-*m*-trifluoromethylaniline from other solvents such as benzene, ethanol and higher boiling petroleum ether (b. p., 60–68°) were unsuccessful because of the extreme solubility of the anil.

Anal. Calcd. for $C_{15}H_9NF_6$: N, 4.42. Found: N, 4.51.

m-Trifluoromethylbenzaldehyde oxime was prepared in a customary manner from the aldehyde, hydroxylamine hydrochloride, sodium hydroxide and water. The sample of *m*-trifluoromethylbenzaldehyde used in this experiment had been stored under nitrogen in the dark, but had assumed a deep green color. This color disappeared promptly on reaction with the hydroxylamine. From the reaction mixture on the addition of water was obtained a colorless oil which was extracted with benzene. Fractionation of the dried solution gave 7.6 g. (65%) of yellow oil distilling at 108–110° (15 mm.). Redistillation yielded a colorless oil: b. p., 102–104° (12 mm.); $n^{20}D$ 1.5128; d^{20}_{27}, 1.305.

Anal. Calcd. for $C_8H_6ONF_3$: N, 7.41. Found: N, 7.48 and 7.44.

The *m*-trifluoromethylbenzaldehyde was not examined for antimalarial action.

N-(*p*-Acetaminophenyl)-2,5-dimethylpyrrole.—This compound was prepared in connection with a proposed synthesis of the anil of *m*-trifluoromethylbenzaldehyde and N-(*p*-aminophenyl)-2,5-dimethylpyrrole. A mixture of 25 g. (0.166 mole) of *p*-aminoacetanilide and 19 g. (0.166 mole) of acetonylacetone was heated on a steam-bath for one hour. Crystallization of the cooled, solid reaction product from ethanol gave a 73% yield of plates melting at 207–208°.

Anal. Calcd. for $C_{14}H_{16}ON_2$: N, 12.28. Found: N, 12.45.

This compound showed no antimalarial activity.

2,4-Dinitrophenylhydrazone of 4-Dibenzofuraldehyde.—Incidental to a consideration of the preparation of the anil of *m*-trifluoromethylaniline and 4-dibenzofuraldehyde, the aldehyde was prepared by the following reactions:

$$C_{12}H_8O + n\text{-}C_4H_9Li \longrightarrow 4\text{-}[C_{12}H_7OLi]$$

$$4\text{-}[C_{12}H_7O]Li + C_6H_5N(CH_3)(CHO) \longrightarrow 4[C_{12}H_7O]CHO$$

The general procedure has been described by Wittig.[9] The crude 4-dibenzofuraldehyde was treated, in a customary manner, with 2,4-dinitrophenylhydrazine, and the dinitrophenylhydrazone separated almost at once in a yield of 38.2%, as microscopic yellow needles melting at 297–299°. Recrystallization from a chloroform–dioxane mixture gave the pure 2,4-dinitrophenylhydrazone of 4-dibenzofuraldehyde melting at 301–302°.

Anal. Calcd. for $C_{19}H_{11}O_5N_4$: N, 14.91. Found: N, 14.96.

4-(*m*-Trifluoromethylbenzalamino)-dibenzofuran.—A solution of one gram (0.00545 mole) of 4-aminodibenzofuran and 0.95 g. (0.00545 mole) of *m*-trifluoromethylbenzaldehyde was refluxed for eight hours. Then, after removal of the benzene, the residual red oil was heated in an oil-bath at 120–130° for one hour. Successive crystallizations of the solid reaction product from benzene–petroleum ether (b. p., 28–38°), chloroform–petroleum ether, and anhydrous ethanol–petroleum ether gave 0.532 g. (29%) of 4-(*m*-trifluoromethylbenzalamino)-dibenzofuran melting at 81–83°.

Anal. Calcd. for $C_{20}H_{12}ONF_3$: N, 4.13. Found: N, 4.17 and 4.25.

m-(γ-Diethylaminopropylamino)-trifluoromethylbenzene.—A mixture of 10 g. (0.062 mole) of *m*-trifluoromethylaniline, 11.5 g. of the hydrochloride of γ-diethylaminopropyl chloride, and a trace of copper powder was heated in an oil-bath at 135–140° for five hours. The mixture was dissolved in a minimum of 20% hydrochloric acid, filtered, and then made alkaline with ammonium hydroxide. Ether extraction, followed by distillation, gave 4.6 g. (27%) of a light yellow mobile liquid which boiled at 171–175° (23 mm.).

Anal. Calcd. for $C_{14}H_{21}NF_3$: N, 10.22. Found: N, 10.12.

m-Trifluoromethylphenylarsonic Acid.—To a stirred mixture of 40 g. sodium arsenite, 0.5 g. copper sulfate and 500 g. of sodium carbonate dissolved in 12 liters of water

(5) Simons and Ramler, THIS JOURNAL, **65**, 389 (1943).

(6) Smith and Bayliss, *J. Org. Chem.*, **6**, 437 (1941).

(7) Fieser and Jones, "Organic Syntheses," **20**, 66 (1940).

(8) Gilman and Schulze, THIS JOURNAL, **47**, 2002 (1925).

(9) Wittig, *Angew. Chem.*, **53**, 293 (1941). See Gilman, Cheney, and Willis, THIS JOURNAL, **61**, 951 (1939) for the preparation of 4-dibenzofuryllithium from dibenzofuran.

and cracked ice was added slowly the diazonium solution prepared from 32.2 g. (0.2 mole) of *m*-trifluoromethylaniline in 1500 cc. of normal hydrochloric acid. The resulting solution was stirred for two hours, allowed to stand at room temperature for six hours, and then filtered. Acidification of the filtrate which had been concentrated to two liters, precipitated the *m*-trifluoromethylphenylarsonic acid. An additional quantity was obtained by further concentration of the aqueous solution. Crystallization from 25% ethanol yielded 28 g. (51%) of arsonic acid melting at 137–138°.

Anal. Calcd. for $C_7H_6O_3F_3As$: As, 27.77. Found: As, 27.35 and 27.28.

6-Nitro-7-trifluoromethylquinoline.—To a mixture of 41 g. (0.2 mole) of 3-amino-6-nitrotrifluoromethylbenzene,[10] 29 g. (0.2 mole) of arsenic acid and 53 g. (0.65 mole) of glycerol, was added (slowly and with vigorous stirring) 56 g. of concentrated sulfuric acid. After having been stirred for two hours, the mixture was refluxed gently for two hours, cooled, and then poured upon cracked ice to give 50 g. of material melting at 151–155°. Two recrystallizations from ethanol gave 27 g. (56%) of product melting at 164–165°.

Anal. Calcd. for $C_{10}H_5O_2N_2F_3$: N, 11.57. Found: N, 11.76.

6-Amino-7-trifluoromethylquinoline.—To a solution containing 10 g. (0.04 mole) of 6-nitro-7-trifluoromethylquinoline and 50 cc. of concentrated hydrochloric acid was added slowly 60 g. (0.26 mole) of stannous chloride in 50 cc. of concentrated hydrochloric acid. The solid material obtained after cooling, filtering and washing with a small quantity of concentrated hydrochloric acid, was suspended in 50 cc. of water and 40% sodium hydroxide was added to strong alkalinity. The filtered and dried material was extracted with a minimum of ethanol, and to the hot ethanolic solution was added water to incipient turbidity. On cooling, there separated 8 g. (92%) of product melting at 152–153°. Recrystallization from benzene–petroleum ether (b. p., 80–110°) gave the compound melting at 154–155°.

Anal. Calcd. for $C_{10}H_7N_2F_3$: N, 13.21. Found: N, 13.48.

6-(2,5-Dimethylpyrryl)-7-trifluoromethylquinoline.—A solution of 5 g. (0.025 mole) of 6-amino-7-trifluoromethylquinoline and 3 g. (0.029 mole) of acetonylacetone in 10 cc. of absolute ethanol and one drop of concentrated hydrochloric acid was refluxed for twenty-two hours. Distillation under reduced pressure gave 3.3 g. (46%) of product distilling at 135–138° (1 mm.). This distillate solidified on standing, and crystallization from dilute ethanol gave a product melting at 86–87°.

Anal. Calcd. for $C_{16}H_{13}N_2F_3$: N, 9.66. Found: N, 9.90.

7-Trifluoromethylquinoline.—A solution of one g. (0.005 mole) of 6-amino-7-trifluoromethylquinoline, 2.5 cc. of concentrated hydrochloric acid and 20 cc. of water was diazotized by the addition of 0.005 mole of sodium nitrite in 5 cc. of water. To the cold diazonium solution was added 2 g. of a 50% hypophosphorous acid solution. A picrate was formed from the solid reaction product, and this was shown, by the method of mixed melting points, to be identical with the picrate of 7-trifluoromethylquinoline.[11a]

3-Trifluoromethylpyrazolone-5.—To 10 g. (0.054 mole) of ethyl trifluoroacetoacetate suspended in 20 cc. of hot water was added dropwise about 2.6 cc. of hydrazine hydrate. The resulting clear solution was cooled; and since only a few crystals separated, the solution was concentrated and then allowed to stand in a desiccator. Crystallization of the oily residue from water yielded 3.8 g. (46.3%) of product melting at 208–209.5°. On recrystallization from hot water, the melting point was 208.5–209.2°.

Anal. Calcd. for $C_4H_3ON_2F_3$: N, 18.42. Found: N, 18.26 and 18.52.

1-Phenyl-3-trifluoromethylpyrazolone-5 was prepared in 43% yield by the procedure of Swarts[11b] by interaction of ethyl trifluoroacetoacetate with phenylhydrazine. The related 1-phenyl-3-methylpyrazolone-5, which was also tested and found to be inactive, was prepared in 70% yield from ethyl acetoacetate and phenylhydrazine in accordance with the procedure of Knorr.[11c]

Other Compounds.—In addition to the compounds containing the trifluoromethyl group which have already been mentioned, the following compounds were also tested in experimental avian malaria: *m*-trifluoromethylacetanilide, m-$CF_3C_6H_4NHCOCH_3$[12]; trifluoroacetanilide, C_6H_5-$NHCOCF_3$[13]; bis-(*m*-trifluoromethyl)-azobenzene, $(m\text{-}CF_3C_6H_4N{=})_2$[13]; *m*-trifluoromethylbenzoic acid, m-$CF_3C_6H_4CO_2H$[5]; 3-trifluoromethyl-4-nitroaniline, $3\text{-}CF_3\text{-}4\text{-}NO_2\text{-}C_6H_3NH_2$; 2,2,2-trifluoroethylamine hydrochloride, $CF_3CH_2NH_2\cdot HCl$[14]; 5-trifluoromethylquinoline, $5\text{-}CF_3C_9H_6N$[15] 7-trifluoromethylquinoline, $7\text{-}CF_3C_9H_6N$[15]; 2-*p*-tolyl-7-trifluoromethylquinoline, $2\text{-}(p\text{-}CH_3C_6H_4)\text{-}7\text{-}CF_3C_9H_5N$[15]; 2-(*m*-trifluoromethylphenyl)-quinoline, $2\text{-}(m\text{-}CF_3C_6H_4)C_9H_6N$[16]; 2-(*m*-trifluoromethylphenyl)-8-methylquinoline, $2\text{-}(m\text{-}CF_3C_6H_4)\text{-}8\text{-}CH_3C_9H_5N$[16]; 1-(*m*-trifluoromethylphenyl) 2,5-dimethylpyrrole.[17] The authors are grateful to Parke, Davis and Company for arranging for the tests, and to D. Blume and R. G. Jones for other assistance.

Summary

Some compounds containing the trifluoromethyl group have been prepared and examined in experimental avian malaria. Of the several compounds, *m*-trifluoromethylphenylarsonic acid shows activity, but the specific contribution of the trifluoromethyl group to such action is uncertain.

AMES, IOWA RECEIVED DECEMBER 11, 1945

(10) Swarts, *Bull. acad. roy. med. Belg.*, **13**, 346 (1927).

(11) (a) See Gilman and Blume, THIS JOURNAL, **65**, 2467 (1943); (b) Swarts, *Bull. acad. roy. Belg.*, (5) **12**, 679 (1926) [*Chem. Zentr.*, **98**, I, 1287 (1927)]; (c) Knorr, *Ber.*, **16**, 2597 (1883).

(12) Swarts, *Bull. acad. roy. med. Belg.*, [3] **35**, 392 (1898).

(13) Swarts, *ibid.*, [5] **8**, 343 (1922).

(14) Gilman and Jones, THIS JOURNAL, **65**, 1458 (1943).

(15) Gilman and Blume, *ibid.*, **65**, 2467 (1943).

(16) Gilman and Woods, *ibid.*, **66**, 1981 (1944).

(17) Gilman, Stuckwisch and Nobis, *ibid.*, **68**, 326 (1946).