

with each alkaloid could be isolated. Each of the salts mutarotated to equilibrium values which were equal mixtures of the two diastereoisomeric salts. Strychnine gave a salt which showed no mutarotation and yielded no active acid.

3. By careful decomposition with hydrochloric acid, the *l*-acid was isolated. It racemized rapidly in organic solvents. The sodium salt racemized much more rapidly in absolute alcohol than in water.

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STEREOCHEMISTRY OF DIPHENYL. XXIV.¹
PREPARATION AND PROPERTIES OF 2,2'-DIFLUORO-3,3'-
DICARBOXY-6,6'-DIMETHOXYDIPHENYL

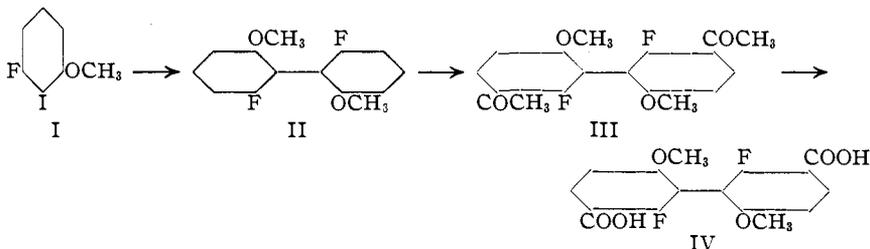
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The small size of the fluorine atom and, as shown in the previous paper, the similarly small size of the methoxyl group,^{1e} made particularly interesting a study of the properties of properly substituted 2,2',6,6'-tetrafluoro-, 2,2',6,6'-tetramethoxy- and 2,6-difluoro-2,6'-dimethoxydiphenyls. On the assumption that the methoxyl is about the same size as the fluorine and calculating the interference possibilities as previously described,³ none of these three compounds should be capable of resolution.

A representative of the last type has been prepared and is described in this communication. The compound is 2,2'-difluoro-3,3'-dicarboxy-6,6'-dimethoxydiphenyl (IV).



It was prepared (1) by the condensation with copper of 1-fluoro-2-iodo-3-methoxybenzene to 2,2'-difluoro-6,6'-dimethoxydiphenyl (II), (2) by in-

¹ The last five papers in this series are as follows: (a) Hill and Adams, *THIS JOURNAL*, **53**, 3453 (1931); (b) Woodruff and Adams, *ibid.*, **54**, 1977 (1932); (c) White and Adams, *ibid.*, **54**, 2104 (1932); (d) Roll and Adams, *ibid.*, **45**, 2494 (1932); (e) Yuan and Adams, *ibid.*, **54**, 2966 (1932).

² This communication is a portion of a thesis submitted by B. C. Becker in partial fulfilment of the requirements for the degree of Doctor of Philosophy in Chemistry at the University of Illinois.

³ Stanley and Adams, *THIS JOURNAL*, **52**, 1200 (1930).

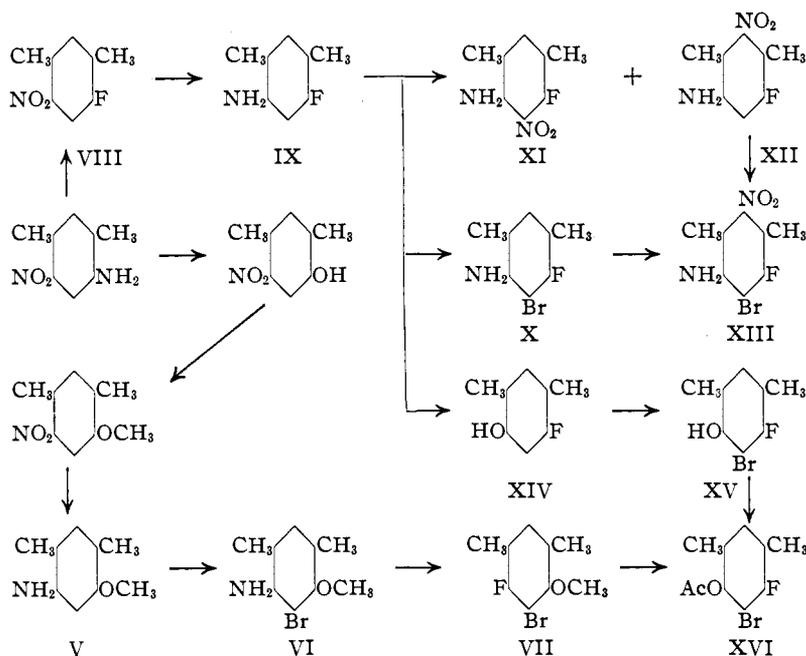
roduction of two aceto groups by means of aluminum chloride and acetyl chloride to 2,2'-difluoro-3,3'-diaceto-6,6'-dimethoxydiphenyl (III), (3) by oxidation of the diaceto derivative by means of sodium hypochlorite to 2,2'-difluoro-3,3'-dicarboxy-6,6'-dimethoxydiphenyl (IV). The various alkaloid salts—brucine, strychnine, morphine, cinchonine and quinine—were all prepared. In no instance was more than a single salt obtained and none of these showed mutarotation even at low temperatures or gave an active acid on decomposition. It appears then that this is truly a representative of a 2,2',6,6'-tetrasubstituted diphenyl in which the ortho substituents do not interfere sufficiently to allow resolution.

Before the above compound was prepared, a number of proper intermediate compounds were synthesized, but all attempts to convert them to the corresponding diphenyls were unsuccessful. These will be described briefly. It was found impossible to obtain 1-fluoro-2-nitro-3-methoxybenzene from 1-fluoro-3-methoxybenzene by nitrating according to the procedure found successful for nitrating 1-fluoro-3-hydroxybenzene.

1-Fluoro-2,4-dimethyl-5-methoxy-6-bromobenzene (VII) was prepared by bromination of 1-amino-2,4-dimethyl-5-methoxybenzene (V) and replacement of the amino group in the 1-amino-2,4-dimethyl-5-methoxy-6-bromobenzene (VI) by fluorine. From the product (VII) attempts to fill the last position in the ring with a nitro or aceto group, to form the Grignard reagent, or to carry out an Ullmann reaction were all unsuccessful.

1-Fluoro-2,4-dimethyl-5-nitrobenzene (VIII) was prepared from the corresponding amino compound by introduction of a fluorine in place of the amino group. It was converted by reduction to 1-fluoro-2,4-dimethyl-5-aminobenzene (IX), which was brominated to 1-fluoro-2,4-dimethyl-5-amino-6-bromobenzene (X). 1-Fluoro-2,4-dimethyl-5-aminobenzene (IX) was nitrated in sulfuric acid to a mixture of the 1-fluoro-2,4-dimethyl-5-amino-6-nitrobenzene (XI) and 1-fluoro-2,4-dimethyl-5-amino-3-nitrobenzene (XII). The 1-fluoro-2,4-dimethyl-5-amino-3-nitrobenzene (XII) was then brominated to 1-fluoro-2,4-dimethyl-3-nitro-5-amino-6-bromobenzene (XIII), identical with the product obtained by nitration of 1-fluoro-2,4-dimethyl-5-amino-6-bromobenzene (X). Attempts to replace the amino group in 1-fluoro-2,4-dimethyl-3-nitro-5-amino-6-bromobenzene (XIII) by hydroxyl or methoxyl were unsuccessful, though no difficulty was encountered in replacing the amino group by chlorine.

1-Fluoro-2,4-dimethyl-5-aminobenzene (IX) was diazotized and converted to 1-fluoro-2,4-dimethyl-5-hydroxybenzene (XIV) which was brominated to 1-fluoro-2,4-dimethyl-5-hydroxy-6-bromobenzene (XV). This product gave an acetyl derivative (XVI), identical with that obtained by demethylating and acetylating 1-fluoro-2,4-dimethyl-5-methoxy-6-bromobenzene (VII).



Experimental⁴

1-Fluoro-2-iodo-3-methoxybenzene.⁵—This product has been described by Hodgson and Nixon. In this investigation it was prepared by the same series of reactions, 3-nitroaniline \rightarrow 1-fluoro-3-nitrobenzene \rightarrow 1-fluoro-3-aminobenzene \rightarrow 1-fluoro-3-hydroxybenzene \rightarrow 1-fluoro-2-nitro-3-hydroxybenzene \rightarrow 1-fluoro-2-nitro-3-methoxybenzene \rightarrow 1-fluoro-2-amino-3-methoxybenzene \rightarrow 1-fluoro-2-iodo-3-methoxybenzene. Since the previous authors give no details, a comment or two on each step may be serviceable to others.

3-Nitroaniline was converted into the corresponding diazonium fluoroborate in the usual way. The yield was 79%. The product, light brown crystals in crude form, could be purified by dissolving in methyl alcohol and precipitating with ethyl ether. White crystals were formed which decomposed at 170–175° after darkening at 145°.

The fluoroborate was decomposed as slowly as possible by careful heating *in vacuo*, then by heating thoroughly to drive over all the product. After alkali washing and steam distillation, a 50% yield of 1-fluoro-3-nitrobenzene of b. p. 197–202° at 750 mm. was obtained.

1-Fluoro-3-nitrobenzene was reduced in the usual way with iron powder and water in the presence of a little hydrochloric acid. The mixture after neutralization was steam-distilled; yield, 85%, b. p. 185° at 755 mm.

1-Fluoro-3-aminobenzene was converted to the corresponding phenol by following

⁴ The melting points reported in this investigation are uncorrected.

⁵ Hodgson and Nixon, *J. Chem. Soc.*, 880 (1928); *ibid.*, 981 (1931); Swarts, *Bull. acad. roy. Belg.*, 241 (1913); Schiemann and Pillarsky, *Ber.*, **62**, 3035 (1929). The literature constants are as follows: 1-fluoro-3-nitrobenzene, b. p. 200° at 756 mm., m. p. 3.6°; 1-fluoro-3-aminobenzene, b. p. 186° at 753 mm.; 1-fluoro-3-hydroxybenzene, b. p. 177.8° at 760 mm., m. p. 13.7°; 1-fluoro-2-iodo-3-methoxybenzene, b. p. 240° at 756 mm.

the directions of Hodgson and Nixon used for 3-chloro-1-hydroxybenzene;⁶ yield, 76%, b. p. 174° at 753 mm.

1-Fluoro-2-nitro-3-hydroxybenzene was obtained in 50% yield; orange yellow needles, m. p. 39°.

1-Fluoro-2-nitro-3-methoxybenzene was prepared by methylating in dry xylene solution with anhydrous potassium carbonate and dimethyl sulfate. Addition of water and then distillation of most of the xylene gave a product, readily purified from methyl alcohol and then petroleum ether; yield, 80% of white crystals, m. p. 43°.

1-Fluoro-2-amino-3-methoxybenzene was prepared by reduction of a methyl alcoholic solution of the nitro compound with concentrated hydrochloric acid and stannous chloride. It was then made alkaline, steam distilled and extracted with ether. The hydrochloride was precipitated with hydrogen chloride after drying the ether solution; yield of amine hydrochloride 81%.

1-Fluoro-2-iodo-3-methoxybenzene was made from the amine hydrochloride by diazotizing and treating with potassium iodide. The product was extracted with ether and washed with sodium bisulfite; yield, 65%, b. p. 115–125° at 3–6 mm.

2,2'-Difluoro-6,6'-dimethoxydiphenyl.—A mixture of 25 g. (0.1 mole) of 1-fluoro-2-iodo-3-methoxybenzene and 25 g. of copper bronze was placed in a small Pyrex flask fitted with a short air condenser and heated in a metal bath at 180–200° for one hour or until the odor of the iodo compound was no longer detectable. The coupling took place much more rapidly at 210–220° but the yield was slightly less. After the flask had cooled sufficiently, the contents were extracted with 40-cc. portions of hot ethyl alcohol. The alcohol was filtered and allowed to cool. Yellow-white crystals of difluorodimethoxydiphenyl were deposited. Evaporation of the mother liquor gave additional crystals which were more yellow. The total yield of crude product was 10 g. (80%). After recrystallization from petroleum ether and again from ethyl alcohol, there remained 8 g. (65%). By several more recrystallizations from ethyl alcohol, pure white 2,2'-difluoro-6,6'-dimethoxydiphenyl was obtained. It melted at 135–136°.

Anal. (Micro). Calcd. for $C_{14}H_{12}F_2O_2$: C, 67.2; H, 4.84. Found: C, 67.23; H, 4.85.

2,2'-Difluoro-3,3'-diaceto-6,6'-dimethoxydiphenyl.—In a three-necked flask fitted with a mercury-sealed stirrer, a lead to a water trap, and a stopper, 5 g. (0.02 mole) of difluorodimethoxydiphenyl was dissolved in a mixture of 75 cc. of dry carbon disulfide and 25 cc. of acetyl chloride. The solution was cooled in a salt-ice mixture and three 5-g. portions of powdered anhydrous aluminum chloride were introduced at ten-minute intervals. The stirring was continued after the ice-bath had been removed until the contents of the flask had reached room temperature. The carbon disulfide top layer was then decanted from the viscous lower layer which was washed with a fresh portion of carbon disulfide. The lower layer containing the aluminum chloride was slowly poured onto 250 g. of cracked ice. The diacetodifluorodimethoxydiphenyl readily formed a solid mass suspended in the water solution of the aluminum chloride. The solid was filtered and washed repeatedly with water to remove all of the inorganic salts. The yield of the crude material was quantitative (6.7 g.) but was reduced to 90% after recrystallization from methyl alcohol. The diacetodiphenyl formed white crystals melting at 138–139.5°.

Anal. Calcd. for $C_{15}H_{16}F_2O_4$: C, 64.65; H, 4.83. Found: C, 64.92; H, 4.78.

2,2'-Difluoro-3,3'-dicarboxy-6,6'-dimethoxydiphenyl.—The difluorodimethoxydiphenyl was oxidized to the difluorodicarboxydimethoxydiphenyl by means of sodium hypochlorite, according to the general procedure of VanArendonk and Cupery.⁷

⁶ Hodgson, English Patent, 200,714 (1923).

⁷ VanArendonk and Cupery. *THIS JOURNAL*, 53, 3184 (1931).

A solution of 6.7 g. (0.02 mole) of difluorodiacetodimethoxydiphenyl in 250 cc. of methyl alcohol was made alkaline with 20 cc. of 20% sodium hydroxide. This solution was kept cold while alkaline sodium hypochlorite was added slowly. (The sodium hypochlorite was prepared from two 100-cc. portions of 20% sodium hydroxide by passing in chlorine gas in the cold until the reaction to litmus was neutral. A liberal excess (20–30 cc.) of sodium hydroxide was then added to make the solution markedly basic.) Keeping the solutions alkaline and cold (under 30°) was important in preventing ring chlorination. As the sodium hypochlorite solution was added, a cloudiness was produced which disappeared as the diphenic acid was formed from the ω -chlorinated aceto derivative. Before acidifying, the excess hypochlorite was destroyed by bubbling in sulfur dioxide or by adding sodium bisulfite until the solution no longer reacted to starch-iodide paper when acidified. Upon acidification the acid was precipitated as a solid, which was filtered off. Additional acid was obtained from the filtrate by making it alkaline, evaporating the methyl alcohol, and reacidifying. The yield was 5.7 g. (84%). The crude acid was purified by dissolving in sodium hydroxide solution, boiling with norite, and reprecipitating. It could also be crystallized from methyl alcohol; m. p. 285–289° with decomposition. For analysis the acid was dried at 110° for twelve hours.

Anal. Calcd. for $C_{16}H_{12}F_2O_6$: neut. equiv., 169; C, 56.8; H, 3.58. Found: neut. equiv., 173.5; C, 56.9; H, 3.71.

Alkaloid Salts of 2,2'-Difluoro-6,6'-dimethoxy-3,3'-dicarboxydiphenyl

Brucine Salt.—When 0.58 g. of anhydrous brucine dissolved in 30 cc. of ethyl alcohol was added to 0.50 g. of the diphenic acid in 80 cc. of ethyl alcohol, a white amorphous precipitate was formed. This weighed 0.86 g. or 80% of the calculated total weight of salt formed. There was no loss of weight on heating to 110° *in vacuo*, hence no solvation.

Rotation. 0.0205 g. made up to 5.4 cc. with pyridine gave $\alpha_D -0.26^\circ$; $l = 1$; $[\alpha]_D^{25} -68.5^\circ$.

The monobrucine salt was also prepared in ethyl acetate in a similar manner. A distinctly crystalline product formed to the amount of 70% in the first fraction. The weight of the residual material brought the total to 82%. The crystalline fraction 0.0226 g. made up to 10 cc. with pyridine gave $\alpha_D 0.31^\circ$; $l = 2$; $[\alpha]_D^{25} -68.7^\circ$. The residual fraction gave $[\alpha]_D^{25} -61.4^\circ$. The first fraction was washed with warm dry ethyl acetate and dried.

Rotation. 0.0205 g. made up to 10 cc. with pyridine gave $\alpha_D -0.27^\circ$; $l = 2$; $[\alpha]_D^{25} -65.8^\circ$.

Anal. (Micro). Calcd. for $C_{39}H_{38}F_2N_2O_{10}$: N, 3.83. Found: N, 3.92.

Decomposition of the salt was carried out at 0–5°. A solution of 0.1 g. of the monobrucine salt in 30 cc. of chloroform was shaken with 100 cc. of ice water to which 2 cc. of concentrated hydrochloric acid had been added. The free diphenic acid was insoluble in both layers and was precipitated as fast as it was formed. After fifteen minutes of shaking the suspension was filtered and the free acid was dried over calcium chloride in a vacuum desiccator. The weight was 0.041 g. (calcd. 0.046). The acid was essentially pure, m. p. 280°, and was used without recrystallization. It gave no rotation in pyridine.

An attempt was made to determine if the newly formed salt showed any evidence of mutarotation. Into a 1-dm. rotation tube enclosed in case for cooling or heating, 0.0394 g. of anhydrous brucine dissolved in 7 cc. of pyridine was introduced. Rotation was taken at 25° and again at 0°, $\alpha_D -0.70^\circ$ and -0.71° ; $[\alpha]_D^{25} -124^\circ$ and $[\alpha]_D^0 -128^\circ$. Then, still at 0°, 0.0388 g. (0.005 g. excess) of the diphenic acid was introduced, mixed thoroughly, and a rotation was taken within a period of five minutes: $\alpha_D -0.535^\circ$;

$[\alpha]_D^0$ -51.2° . Rotation, three hours later: α_D -0.535° ; $[\alpha]_D^0$ -51.2° . The tube and its contents were then permitted to warm to room temperature: α_D -0.663° ; $[\alpha]_D^{25}$ -63.4° . (This checks the rotation of the crystalline monobrucine salt.) After twenty-four hours at room temperature the solution was again cooled to 0° . Rotation: α_D -0.540° ; $[\alpha]_D^0$ -51.7° .

No success was encountered in attempting to prepare the dibrucine salt.

Morphine Salt.—The monobasic morphine salt was formed in dry ethyl acetate by the addition of 0.285 g. (0.001 mole) of morphine in 40 cc. of ethyl acetate to 0.338 g. of the diphenic acid in 80 cc. of ethyl acetate. The first fraction separated immediately and amounted to 0.25 g. or 40% of the total weight of salt; the second precipitate was obtained by partial evaporation and cooling, and weighed 0.128 g. (20%). The third fraction, formed on further evaporation, was 14%; and the residue recovered on evaporation to dryness was 10%. The specific rotations of these crude fractions, in 95% ethyl alcohol ($l = 2$) were, respectively, -63.5 , -59.5 , -64.3 and -26° . The low value for the residue was undoubtedly the result of impurities. The first two fractions (0.30 g.) were dissolved in absolute ethyl alcohol, filtered and cooled in carbon dioxide snow. A white precipitate was formed, weighing 0.17 g. and having a coarsely granular appearance under the microscope. A sample of this was dissolved in 95% ethyl alcohol at $0-10^\circ$ and cooled immediately to 0° .

Rotation. 0.0243 g. made up to 10 cc. with ethyl alcohol at 0° gave α_D -0.20° ; $l = 1$; $[\alpha]_D^0$ -82.3° .

The solution in the rotation tube was allowed to come to room temperature 25° : α_D -0.145° ; $[\alpha]_D^{25}$ -59.7° . (This checked the rotation of crude fractions.) The solution was further allowed to stand at $25-30^\circ$ for twenty hours and then cooled again to 0° : α_D -0.19° ; $[\alpha]_D^0$ -78.2° . Analysis of the recrystallized material showed it to be the desired morphine salt.

Anal. (Micro). Calcd. for $C_{33}H_{31}F_2NO_9$; N, 2.25. Found: N, 2.4.

Quinine Salt.—A solution of 0.324 g. of quinine (0.001 mole) in 30 cc. of absolute ethanol was added to 0.338 g. of the diphenic acid dissolved in 30 cc. of absolute alcohol. Evaporation to half volume gave a yellow precipitate weighing 0.05 g. The second fraction, which was a very light yellow amorphous precipitate, weighed 0.26 g. The third or residual fraction was obtained by evaporation to dryness. It was quite yellow and weighed 0.217 g. The total recovered material amounted to 80% of the calculated value. These three fractions gave, respectively, the specific rotations in chloroform at 27° : -69.4 , -83.4 and -75.4° . The intermediate fraction, 0.0736 g., made up to 10 cc. with chloroform gave α_D 1.23; $l = 2$; $[\alpha]_D^{27}$ -83.4° . This fraction was analyzed.

Anal. (Micro). Calcd. for $C_{33}H_{38}F_2N_2O_8$; N, 4.23. Found: N, 4.21.

Strychnine Salt.—A solution of 0.334 g. (0.001 mole) of strychnine in 50 cc. of absolute ethanol was added to 0.338 g. of the diphenic acid dissolved in absolute alcohol. The solution was filtered, evaporated to 40 cc., and cooled with carbon dioxide snow. A precipitate formed and was filtered off. However, on warming to room temperature this material melted and became viscous and sticky. On being placed in a desiccator, it finally hardened to a glassy solid which could be pulverized to a white amorphous powder; weight, 0.101 g.

Rotation. 0.0705 g. made up to 10 cc. with chloroform gave α_D -0.15° ; $l = 2$; $[\alpha]_D^{25}$ -10.6° .

The second fraction of the strychnine salt was obtained by evaporating the ethyl alcohol to about 10 cc. and then adding 70 cc. of ethyl acetate. A white amorphous powder was precipitated. This was filtered off, washed with warm dry ethyl acetate and dried; weight, 0.422 g. (63%). On heating this salt shrank at $180-205^\circ$ and foamed without darkening at $205-220^\circ$.

Rotation. 0.0627 g. made up to 10 cc. with chloroform gave $\alpha_D -0.15$; $l = 2$; $[\alpha]_D^{25} -12^\circ$.

Analysis of the intermediate fraction showed it to be the desired salt. The residue soluble in ethyl acetate was negligible—the amount recovered being too small for a determination of the specific rotation.

Anal. (Micro). Calcd. for $C_{37}H_{34}F_2N_2O_8$: N, 4.16. Found: N, 4.25.

The intermediate fraction of strychnine salt, 0.2 g., was shaken with 50 cc. of 6 *N* hydrochloric acid at -15° . After two hours, the 6 *N* acid was replaced by a fresh 50-cc. portion—the free diphenic acid was filtered off, resuspended in cold hydrochloric acid, and placed in the refrigerator overnight. The free acid was then filtered off, washed free of hydrochloric acid, and dried at room temperature in a vacuum desiccator; weight, 0.093 g. (calcd. 0.101 g.); m. p. 275° . It showed no rotation.

Cinchonine Salt.—A solution of 0.294 g. (0.001 mole) of cinchonine in 30 cc. of absolute ethyl alcohol was added to 0.338 g. of the diphenic acid dissolved in 30 cc. of absolute alcohol. The solution was filtered, evaporated to 15 cc. and 50 cc. of ethyl acetate was added. A precipitate was formed, weighing 0.43 g.

Rotation. 0.0654 g. made up to 10 cc. with 95% ethyl alcohol gave $\alpha_D +1.08^\circ$; $l = 2$; $[\alpha]_D^{25} 82.7^\circ$.

The filtrate was evaporated to dryness to give a yellow amorphous material weighing 0.189 g.

Rotation. 0.0490 g. made up to 10 cc. with 95% ethyl alcohol gave $\alpha_D 0.75^\circ$; $l = 2$; $[\alpha]_D^{25} 76.5^\circ$.

Another run of 0.294 g. of cinchonine and 0.338 g. of acid in 60 cc. of absolute alcohol gave three fractions on the slow evaporation of the alcohol. Of these, the intermediate fraction, weighing 0.114 g. was white and amorphous.

Rotation. 0.0436 g. made up to 10 cc. with ethyl alcohol gave $\alpha_D 0.733^\circ$; $l = 2$; $[\alpha]_D^{25} 84.1^\circ$. Analysis of this fraction showed it to be the desired monochinchonine salt.

Anal. (Micro). Calcd. for $C_{35}H_{34}F_2N_2O_7$: N, 4.43. Found: N, 4.30.

1-Fluoro-3-methoxybenzene.—A solution of 123 g. (1 mole) of 1-amino-3-methoxybenzene in a mixture of 280 cc. of concentrated hydrochloric acid, and 500 g. of ice was diazotized at $0-5^\circ$ by the addition of 69 g. of sodium nitrite in 160 cc. of water. The diazotized mixture was filtered if necessary and a minimum of 170 cc. of fluoboric acid solution was added. The precipitated diazonium fluoborate of 1-amino-3-methoxybenzene was filtered off and washed successively with 10–20 cc. of fluoboric acid solution, 70 cc. of ethyl alcohol, and 70 cc. of ethyl ether. The weight of dry diazonium salt was 170 g. (76%). This was quite unstable as compared with the corresponding 3-nitrodiazonium salt and unless it was kept very dry, it decomposed spontaneously over a period of twenty-four to forty-eight hours.

The diazonium salt was decomposed immediately without purification in a dry flask connected through a condenser and wash bottle to a water aspirator. Heat was applied to one part of the flask to start the decomposition; and the reaction was allowed to proceed spontaneously. Sometimes cooling was necessary if decomposition was too rapid. Finally, when the reaction subsided, the flask was heated strongly while the system was evacuated. The distillate and the water in the wash bottles were mixed, neutralized with sodium carbonate, filtered and extracted with ethyl ether. The 1-fluoro-3-methoxybenzene (b. p. 158° at 743 mm.) was a colorless mobile liquid of characteristic anisole-like odor. The yield was 53 g. (42%); $d_{20}^{20} 1.107$, $n_D^{20} 1.4892$.

Anal. (Micro). Calcd. for C_7H_7FO : C, 66.6; H, 5.60. Found: C, 66.77; H, 5.52.

1-Fluoro-2-nitro-3-methoxybenzene.—Attempts to prepare 1-fluoro-2-nitro-3-methoxybenzene by sulfonation and nitration of 1-fluoro-3-methoxybenzene as de-

scribed for the preparation of 1-fluoro-2-nitro-3-hydroxybenzene from 1-fluoro-2-nitro-3-hydroxybenzene were unsuccessful.

1-Amino-2,4-dimethyl-5-methoxy-6-bromobenzene Hydrobromide.—To a solution of 50 g. (0.33 mole) of 1-amino-2,4-dimethyl-5-methoxybenzene⁸ in 250 cc. of glacial acetic acid, was added slowly 53 g. of bromine in 25 cc. of acetic acid. On cooling the mixture, fine white crystals of the brominated amine hydrobromide were precipitated. The precipitate was filtered and washed with 25–50 cc. of glacial acetic acid. The salt was dried at 110°. The yield depended upon the volume of acetic acid used; the pure product usually weighed about 78 g. (75%); m. p. 187° with decomposition. By evaporation of the acetic acid filtrate, the remaining impure material could be obtained. (Acetyl derivative of the free base, from dilute alcohol, m. p. 147–148°.) A small amount of the acetyl derivative was always formed when recrystallizing the amine hydrobromide from glacial acetic acid.

Anal. Calcd. for $C_9H_{13}Br_2NO$: Br (ionizable), 25.71. Found: Br, 25.69.

1-Fluoro-2,4-dimethyl-5-methoxy-6-bromobenzene.—A solution was made of 31.1 g. (0.1 mole) of the 1-amino-2,4-dimethyl-5-methoxy-5-bromobenzene hydrobromide in 10 cc. of concentrated hydrochloric acid and 25 cc. of water. The mixture was cooled to 0–5° and diazotized slowly with 6.9 g. of sodium nitrite in 15 cc. of water. After being allowed to stand for fifteen minutes, the solution was filtered and 17–25 cc. of cold fluoboric acid solution was added. The diazonium fluoborate was precipitated, filtered off, and washed successively with 5 cc. of fluoboric acid solution, 10 cc. of ethyl alcohol and 10 cc. of ethyl ether. The dry salt weighed 23 g. (70%). It was a pale yellow solid, quite soluble in water and fairly stable when dry. The decomposition temperature was about 105°. The desired fluoro compound was obtained from this diazonium salt by dry distillation in a flask connected to a condenser and wash bottles. The flask was gently heated to start the decomposition. If the reaction became so rapid as to tend to build up an internal pressure, the flask was externally cooled with tap water. After the diazonium salt was decomposed, the fluoro compound remaining in the flask was distilled under reduced pressure. The product weighed 12.2 g. (52%) based on the original amine hydrobromide. 1-Fluoro-2,4-dimethyl-5-methoxy-6-bromobenzene is a heavy colorless liquid of faint odor; b. p. 125° at 15 mm., n_D^{20} 1.5802, d_4^{20} 1.4350.

Anal. (Parr bomb). Calcd. for $C_9H_{10}BrFO$: Br, 34.3. Found: Br, 33.9.

Attempts to nitrate the molecule and replace the last vacant position were unsuccessful.

The Ullmann reaction with copper or zinc was unsatisfactory and the Grignard reagent could not be formed.

With aluminum chloride and acetic anhydride in carbon disulfide no reaction took place at low temperature, but heated to the boiling point of the reaction mixture, 1-fluoro-2,4-dimethyl-5-acetoxy-6-bromobenzene (described below) was formed.

1-Fluoro-2,4-dimethyl-5-nitrobenzene.—To 135 cc. of cold concentrated sulfuric acid 24.2 g. (0.2 mole) of 1-amino-2,4-dimethylbenzene was slowly added. The mixture was stirred until all of the amine sulfate dissolved and it was then cooled to 0–10° and 20 g. or 14.5 cc. (10% excess) of nitric acid (sp. gr. 1.42) was added. After standing for fifteen minutes, the solution was diluted with 400 g. of ice. The nitrated 1-amino-2,4-dimethylbenzene sulfate⁹ precipitated but was not isolated.

The suspension was immediately diazotized by the addition of 13.8 g. of sodium nitrite in 30 cc. of water. After the diazotization mixture had stood for fifteen minutes,

⁸ Boyce, Rankine and Robertson, *J. Chem. Soc.*, 1216 (1930).

⁹ Nörling and Collin, *Ber.*, 17, 265 (1884).

34–40 cc. of cold fluoboric acid was added. The precipitated diazonium fluoborate was filtered off, washed with ethyl alcohol and ether and dried. The weight was 28.2 g. (53% based on 1-amino-2,4-dimethylbenzene used). The dry diazonium fluoborate was quite stable; its decomposition temperature was 130°.

The salt was placed in a distilling flask connected to a condenser and wash bottles and decomposed as described for the other fluoborates. The product boiled at 133° at 30 mm.; 234° at 750 mm. The yield was 9.5 g. (53% based on the diazonium salt). The 1-fluoro-2,4-dimethyl-5-nitrobenzene was a pale yellow, heavy liquid; d_{20}^{20} 1.230, n_D^{20} 1.532.

Anal. (Micro). Calcd. for $C_8H_8FNO_2$: N, 8.28. Found: N, 8.10.

1-Fluoro-2,4-dimethyl-5-aminobenzene.—A mixture of 17.0 g. (0.1 mole) of 1-fluoro-2,4-dimethyl-5-aminobenzene, 25 g. of iron powder, 25 cc. of water and 5 cc. of dilute hydrochloric acid was placed in a 500-cc. flask fitted with a reflux condenser, and heated with shaking until the water refluxed from the heat of reaction. The reduction was completed by heating on the steam-bath for an hour, with the occasional addition of 1–2 cc. of dilute hydrochloric acid. The contents of the flask were neutralized with a few cubic centimeters of 20% sodium hydroxide solution and the 1-fluoro-2,4-dimethyl-5-aminobenzene steam distilled. The product separated from the steam distillate in white plates which turned pink or brown on contact with the air. It was purified by recrystallization from petroleum ether and then sublimation to give white plates melting at 57–58° (acetyl derivative from dilute alcohol, m. p. 133–134°).

Anal. (Micro). Calcd. for $C_8H_{10}FN$: N, 10.07. Found: N, 9.74.

1-Fluoro-2,4-dimethyl-5-amino-6-bromobenzene.—By addition of one mole equivalent of bromine to an acetic acid solution of 1-fluoro-2,4-dimethyl-5-aminobenzene, the hydrobromide of the 1-fluoro-2,4-dimethyl-5-amino-6-bromobenzene separated. The salt was readily recrystallized from glacial acetic acid. It decomposed without melting at 220°. The free base was purified by recrystallization from methyl alcohol and was obtained in white crystals melting at 56° (acetyl derivative from dilute alcohol, m. p. 170–171°).

Anal. (Volhard). Hydrobromide salt: Calcd. for $C_8H_{10}Br_2FN$: Br (ionized), 26.74. Found: Br, 26.85.

Nitration of 1-Fluoro-2,4-dimethyl-5-aminobenzene: 1-Fluoro-2,4-dimethyl-5-amino-3-nitrobenzene and 1-Fluoro-2,4-dimethyl-5-amino-6-nitrobenzene.—When 1-fluoro-2,4-dimethyl-5-aminobenzene was nitrated in concentrated sulfuric acid, two products were obtained. These were separated by their difference in solubility in petroleum ether. The less soluble nitration product, which was formed in smaller amounts, could be recrystallized from petroleum ether to give orange red crystals which melted at 88–89° (acetyl derivative from alcohol, m. p. 148–149°). This was identified by bromination in acetic acid to give 1-fluoro-2,4-dimethyl-3-nitro-5-amino-6-bromobenzene which was identical (m. p. 106°) with the product prepared by brominating first and then nitrating, as described in the next paragraph.

Anal. Calcd. for $C_8H_8FN_2O_2$: N, 15.2. Found: N, 15.29.

The more soluble part was recrystallized several times from petroleum ether to give a dark red compound melting at 72–74° (acetyl derivative from alcohol, m. p. 193–194°). Analysis of the amine indicated that it was an isomeric mononitro derivative, 1-fluoro-2,4-dimethyl-5-amino-6-nitrobenzene.

Anal. Calcd. for $C_8H_8FN_2O_2$: N, 15.2. Found: N, 14.76. The analysis of the acetyl derivative, which could be obtained in a purer form, confirmed this formula.

Anal. Calcd. for $C_{10}H_{11}FN_2O_3$: N, 12.38. Found: N, 12.34.

1-Fluoro-2,4-dimethyl-3-nitro-5-amino-6-bromobenzene.—To a solution of 10.9 g. (0.05 mole) of 1-fluoro-2,4-dimethyl-5-amino-6-bromobenzene in 25 cc. of cold concentrated sulfuric acid was added 1.4 cc. of nitric acid (sp. gr. 1.42) in 25 cc. of concentrated sulfuric acid. After standing for thirty minutes in the cold, the nitration mixture was poured onto 150 g. of cracked ice. The free amine precipitated, and was purified by recrystallization from petroleum ether giving a bright yellow solid, m. p. 105.5–106°.

Anal. (Micro). Calcd. for $C_8H_8BrFN_2O_2$: N, 10.65. Found: N, 10.72.

The attempts to replace the amino groups through the diazonium salt by hydroxyl or methoxyl were unsuccessful, though a chlorine could thus be introduced readily.

1-Fluoro-2,4-dimethyl-3-nitro-5-chloro-6-bromobenzene.—A solution of 1.3 g. (0.005 mole) of 1-fluoro-2,4-dimethyl-3-nitro-5-amino-6-bromobenzene in 12 cc. of cold hydrochloric acid was diazotized with 0.35 g. of sodium nitrite in 5 cc. of water. A solution of cuprous chloride in concentrated hydrochloric acid was then added and the 1-fluoro-2,4-dimethyl-3-nitro-5-chloro-6-bromobenzene precipitated. By purification from ethyl alcohol, white crystals were obtained, m. p. 113.5–114°.

Anal. (Parr bomb). Calcd. for $C_8H_8BrClFNO_2$: Cl + Br, 40.85. Found: Cl + Br, 40.7.

1-Fluoro-2,4-dimethyl-5-hydroxybenzene.—A solution of 2.8 g. (0.02 mole) of 1-fluoro-2,4-dimethyl-5-aminobenzene in 6 cc. of concentrated sulfuric acid and 12 g. of ice was diazotized with 1.4 g. of sodium nitrite in 6 cc. of water. The diazonium salt was decomposed to the phenol by dropping its solution slowly into a boiling mixture of 10 cc. of concentrated sulfuric acid and 7 cc. of water. The 1-fluoro-2,4-dimethyl-5-hydroxybenzene was steam distilled and extracted from the distillate with ethyl ether. The yield was 2.4 g. (85%). The phenol was purified by sublimation to give a white solid melting at 44–45°.

Anal. Calcd. for C_8H_8FO : C, 68.54; H, 6.48. Found: C, 68.41; H, 6.44.

1-Fluoro-2,4-dimethyl-5-hydroxy-6-bromobenzene.—The product was obtained by bromination of 1-fluoro-2,4-dimethyl-5-hydroxybenzene in glacial acetic acid. The product obtained by dilution of the reaction mixture was recrystallized from ethyl alcohol, m. p. 65–68°. This product was identical with that obtained by demethylation and simultaneous acetylation of the corresponding methyl ether previously described. It was purified from 50% ethyl alcohol, m. p. 75–76°.

Anal. (Micro) of the phenol and the acetyl derivative. Calcd. for C_8H_8BrFO : Br, 36.5. Found: Br, 36.7. Calcd. for $C_{10}H_{10}BrFO_2$: Br, 30.6. Found: Br, 30.8.

An attempt to nitrate the 1-fluoro-2,4-dimethyl-5-hydroxy-6-bromobenzene was unsuccessful.

Summary

1. 2,2'-Difluoro-3,3'-dicarboxy-6,6'-dimethoxydiphenyl has been synthesized. 1-Fluoro-2-iodo-3-methoxybenzene was condensed with copper to 2,2'-difluoro-6,6'-dimethoxydiphenyl. By means of acetyl chloride and aluminum chloride, 2,2'-difluoro-3,3'-diaceto-6,6'-dimethyldiphenyl was produced and this substance oxidized by sodium hypochlorite to 2,2'-difluoro-3,3'-dicarboxy-6,6'-dimethoxydiphenyl.

2. The alkaloidal salts showed no mutarotation. Only one form could be obtained of each and no active acids could be obtained by decomposition.