[Contribution from the Laboratory of Radiochemistry, University of Cincinnati]

COMPOUNDS FOR CANCER RESEARCH. III. SOME DERIVATIVES OF 9,9′-BIFLUORYL[1]

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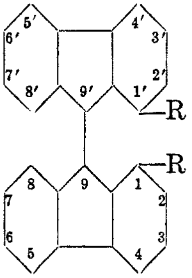
Received April 2, 1948

Derivatives of fluorene have been found to possess important physiological properties. The amino alcohol esters of fluorene-9-carboxylic acid have local anesthetic and antispasmodic action (1, 2), as do the amino alcohol esters of fluorenone-2-carboxylic acid (3). On the other hand 2-aminofluorene and some of its derivatives have been shown to possess carcinogenic properties (4, 5). Pinck (5) has postulated that carcinogenesis is due to the conversion of the latter compound to a bifluorylidene derivative, which then acts as an intermediate for the elaboration of carcinogens.

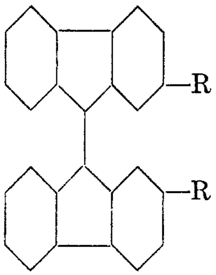
Recently compounds substituted with the strongly basic amidino groups $C{:}NH{\cdot}NH_2$ have attracted considerable attention owing to their therapeutic activity in several protozoal and bacterial diseases such as leishmaniasis, trypanosomiasis (18), and staphylococcal or streptoccal infections. Straight chain aliphatic compounds carrying terminal amidino groups of the type $H_2N{\cdot}NH{:}C{-}(CH_2)_n{-}C{:}NH{\cdot}NH_2$ were found to exhibit a maximum therapeutic activity when n was equal to 11 (20). Blaschko and Duthie have reported (28) that aliphatic amidines have an inhibiting effect on amine oxidase.

The physiological activity, however, is not confined to the aliphatic series. Aromatic compounds of the type $H_2N{\cdot}NH{:}C{-}C_6H_4{-}x{-}C_6H_4{-}C{:}NH{\cdot}NH_2$ where x is a simple aliphatic chain, $-(CH_2)_n-$, a chain with ether $-O-(CH_2)_n-O-$ or with ethylenic linkages, as $-CH{=}CH-$, showed trypanocidal activity (19) and activity against sarcoma 37 in mice (26) and a favorable influence on patients with multiple myeloma (27).

It was therefore of considerable interest to prepare derivatives of 9,9′-bifluoryl substituted symmetrically with amidino groups at the 1,1′ positions, type I, and at the 2,2′ positions, type II.



I



II

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[1] Presented at the meeting of the Ohio Academy of Science, Toledo, Ohio, May 7, 1948.

This work was aided in part by Cancer Research Grant C-341 from the U. S. Public Health Service.

From the M.Sc. thesis of John H. Weisburger, University of Cincinnati, June 1948.

It might be pointed out that in 9,9′-bifluoryl (II), the 2 and 2′ positions are separated by 8 carbon atoms. Hence, some physiological activity might be associated with the molecule. The large molecule might be expected to reduce toxic effects.

9,9′-Bifluoryl may be produced by a variety of methods: Action of heat and sodium acetate on a mixture of fluorene and fluorenone (6); amalgamated zinc on 9-chlorofluorene (7); thioacetic acid on 9-chlorofluorene (8); and spontaneous elimination of iodine between two molecules of 9-iodofluorene, the latter being obtained from 9-chlorofluorene and sodium iodide in acetone (9). Bifluoryl also may be obtained by the reduction of 9,9′-bifluorylidene. The latter is formed in the following reactions: The action of heat and chlorine, bromine, or sulfur on fluorene without a solvent (10), or in a solvent (11); copper (12) or silver (13) on 9,9-dichlorofluorene; potassium hydroxide in acetone on 9-chlorofluorene (14); potassium disulfide-potassium hydroxide on 9,9-dichlorofluorene (15); dehydration of 9-fluorylfluorene-9-ol, the latter being derived from a Grignard reaction of 9-fluorylmagnesium bromide on fluorenone (16); and the decomposition of 9-diazofluorene (17). Despite the fact that there are a number of methods of preparing bifluoryls, only a few derivatives are known.

The starting materials for our syntheses were the well known fluorenone-1- and -2-carboxylic acids. Ray and Kreiser (21) reduced the 9-keto acid to the 9-hydroxy acid with zinc and ammonia in ethanol. Reduction with zinc in aqueous potassium hydroxide, however, resulted in a shorter reaction time and improved yield. Incidentally, an attempt to secure complete reduction of fluorenone-2-carboxylic acid to fluorene-2-carboxylic acid by lengthening the reaction time to eighty-six hours failed.

The 9-chlorofluorene-1- and -2-carbonyl chlorides were obtained from the 9-hydroxy acids by treatment with thionyl chloride and converted into the ethyl esters by reaction with absolute ethanol. The ready preparation of these 9-chloro derivatives suggested the use of Finkelstein's method (9) to join two fluorene nuclei, thereby affording the corresponding bifluoryls.

Attempts to ammonolyze diethyl 9,9′-bifluoryl-1,1′- or 2,2′-dicarboxylate in benzene or ethanol, at room temperature for two months, were unsuccessful. Consequently, the amides were prepared *via* the acids → acid chlorides → amides. Phosphorus oxychloride then converted the amides into the nitriles in good yields (22).

It was found impossible to prepare diethyl 9,9′-bifluoryl-1,1′-dicarbimidate dihydrochloride from 9,9′-bifluoryl-1,1′-dinitrile according to Pinner's method (23). Apparently this nitrile is another ortho substituted nitrile which fails to form an imido ester (24).

9,9′-Bifluoryl-2,2′-dinitrile, however, reacted very readily with absolute ethanol and hydrogen chloride, affording the imido ester, from which 9,9′-bifluoryl-2,2′-dicarboxamidine dihydrochloride was prepared in good yields.

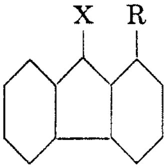
This white compound was easily converted to the red 9,9′-bifluorylidene derivative by air oxidation when precipitated from absolute ethanol with ether (small particle size). It was stable to air oxidation when crystallized slowly from absolute ethanol (large particle size). A later paper will deal with the bifluorylidene derivatives.

The symmetrically disubstituted bifluoryls should exist in *levo*, *dextro*, and *meso* forms since the 9 and 9′ carbons are asymmetric. In this investigation no specific attempt was made to separate the *meso* from the *racemic* form. It was found, however, that after diethyl 9,9′-bifluoryl-1,1′-dicarboxylate had aged for several weeks, recrystallization from ethanol yielded a fraction of m.p. 196–198°. In contrast, the mixture of isomers obtained when this compound was prepared, melted over the range 120–160°. The isomer isolated probably was the racemate. In a similar fashion a high-melting isomer, m.p. 264–267° dec., was separated from the 9,9′-bifluoryl-2,2′-dinitrile mixture, m.p. 110–190°, by recrystallization from acetone and isoamyl alcohol. Ageing of the material seemed to be an important factor, since recrystallization of the compounds shortly after preparation did not result in any definite increase in melting point.

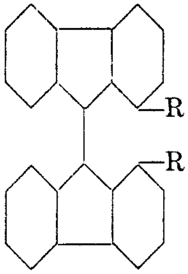
It is of interest to note that the melting points of many bifluoryl derivatives are decomposition points, at which the white bifluoryl compound loses hydrogen and becomes an orange-red bifluorylidene derivative. The latter generally melts to a red liquid. Although these decomposition points are not very sharp, they are nevertheless characteristic of each compound.

In the course of this investigation the following compounds were prepared.

I. Derivatives of the 1,1′-series

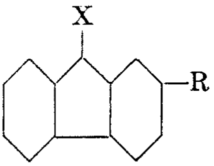


(III), X = =O; R = COOH
(IV), X = OH; R = COOH
(V), X = Cl; R = COCl
(VI), X = Cl; R = $COOC_2H_5$

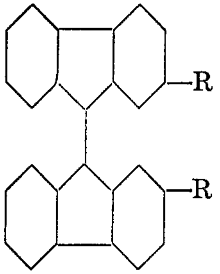


(VII), R = $COOC_2H_5$
(VIII), R = COOH
(IX), R = COCl
(X), R = $CONH_2$
(XI), R = CN

II. Derivatives of the 2,2′-series



(XII), X = =O; R = COOH
(XIII), X = OH; R = COOH
(XIV), X = Cl; R = COCl
(XV), X = Cl; R = $COOC_2H_5$
(XVI), X = Cl; R = $COOCH_3$
(XVII), X = Cl; R = $CONH_2$
(XVIII), X = Cl; R = CN



(XIX), R = $COOC_2H_5$
(XX), R = $COOH$
(XXI), R = $COCl$
(XXII), R = $CONH_2$
(XXIII), R = CN
(XXIV), R = $C(=NH \cdot HCl)OC_2H_5$
(XXV), R = $C(=NH)NH_2 \cdot HCl$

EXPERIMENTAL

All melting points are uncorrected.

9-Hydroxyfluorene-1-carboxylic acid (*IV*). A solution of 85 g. of fluorenone-1-carboxylic acid (III) prepared according to Fieser and Seligman (25), in 1700 cc. of water containing potassium hydroxide (97 g.) was heated to 70°. Zinc dust (100 g.) and copper sulfate (0.5 g.) were added. The mechanically stirred mixture was refluxed for two and one-half hours and the excess zinc then filtered off. The resulting cold, tan solution was neutralized dropwise with dilute hydrochloric acid while stirred mechanically over a period of three hours. Rapid addition of acid tends to produce gums. The pinkish-white acid was filtered, washed and oven-dried at 115°. The yield of acid melting at 191–194° was 80 g. (94%). A sample recrystallized twice from xylene was creamy-white, m.p. 198–199°.

Anal. Calc'd for $C_{14}H_{10}O_3$: C, 74.3; H, 4.45.
Found: C, 74.53; H, 4.43.

9-Chlorofluorene-1-carbonyl chloride (*V*). 9-Hydroxyfluorene-1-carboxylic acid (50 g.) was refluxed with thionyl chloride (250 cc.) until complete solution was effected. The solution was allowed to stand overnight, affording a crop of crystals, m.p. 162–163°, after filtering and washing with ligroin (30–60°).

Anal. Calc'd for $C_{14}H_8Cl_2O$: Cl, 27.0. Found: Cl, 25.92, 26.05.

Evaporation of the thionyl chloride filtrate yielded a further crop of crystals. This material was washed with ligroin and used in the next step.

Ethyl 9-chlorofluorene-1-carboxylate (*VI*). The combined fractions of the acid chloride (V) were heated on a water-bath with absolute ethanol (300 cc.) until all material had dissolved. The ethanol was distilled off, leaving the ester as a dark oil. This was refluxed with two 300-cc. portions of ligroin (30–60°), which were decanted from the oil after one-half hour. The ligroin solution was clarified with Darco and allowed to stand in an ice-bath overnight. A crop of long white needles, weighing 44 g. (73%), was obtained.

A sample recrystallized again from ligroin (30–60°) melted at 56–57°.

Anal. Calc'd for $C_{16}H_{13}ClO_2$: Cl, 13.0. Found: Cl, 12.83, 13.05.

Diethyl 9,9'-bifluoryl-1,1'-dicarboxylate (*VII*). Ethyl 9-chlorofluorene-1-carboxylate (50 g.) in acetone (100 cc.) was added to sodium iodide (65 g.) in acetone (400 cc.). After a few seconds, iodine was liberated and sodium chloride precipitated. The mixture was refluxed for one-fourth hour and allowed to stand overnight. A solution of sodium hydrogen sulfite (50 g.) in 350 cc. of water was added with mechanical stirring to reduce the iodine and precipitate the ester. After stirring the suspension for five minutes, water was added to make a total volume of two and one-half liters, and stirring then continued for one-fourth hour. When the precipitate had settled, it was filtered and washed. The yield of creamy white material, m.p. 120–160°, was 41 g. (95%). A sample recrystallized from ethanol melted at 130–160°. Upon ageing for four weeks, a sample recrystallized again from ethanol melted at 196–198°.

Anal. Calc'd for $C_{32}H_{26}O_4$: C, 81.2; H, 5.5.
Found: C, 80.50, 80.50; H, 5.57, 5.48.

9,9′-Bifluoryl-1,1′-dicarboxylic acid (VIII). The crude ester (VII) (40 g.) was suspended in ethanol (500 cc.) containing potassium hydroxide (11 g.) and refluxed on a water-bath for two hours. Then water (1000 cc.) was added and the suspension heated to near boiling. After filtration, the mechanically stirred yellowish filtrate was acidified at the boiling point. The precipitate was allowed to stand overnight, filtered, and washed. After solution in hot sodium hydrogen carbonate and reprecipitation with dilute hydrochloric acid, 31.5 g. of a white material, m.p. 340° (block) was obtained.

Anal. Calc'd for $C_{28}H_{18}O_4$: C, 80.5; H, 4.32.
Found: C, 79.93, 79.85; H, 4.51, 4.37.

9,9′-Bifluoryl-1,1′-dicarbonyl chloride (IX). The acid (VIII) (27 g.) was refluxed with thionyl chloride (250 cc.) until dissolved. Upon standing overnight the acid chloride crystallized out. After filtering and washing with ligroin (30–60°), 17 g. of white needles, m.p. 272–275° dec. were obtained.

Anal. Calc'd for $C_{28}H_{16}Cl_2O_2$: Cl, 15.6. Found: Cl, 14.63, 14.67.

A less pure material, used in the next step, was obtained from the thionyl chloride filtrate.

9,9′-Bifluoryl-1,1′-dicarboxamide (X). The acid chloride (IX) was treated with ice-cold concentrated ammonium hydroxide (100 cc.). After standing for one hour, 12 g. of light tan amide, m.p. >310° was obtained.

The crystalline acid chloride (IX) (10 g.) similarly yielded 8 g. of analytically pure amide (m.p. >310°). The amide is sparingly soluble in the usual organic solvents.

Anal. Calc'd for $C_{28}H_{20}N_2O_2$: N, 6.73. Found: N, 6.89, 6.83.

9,9′-Bifluoryl-1,1′-dinitrile (XI). The amide (X) (9.5 g.) was added to phosphorus oxychloride (50 cc.). On heating slowly, hydrogen chloride was evolved between 40° and 70°, and the amide dissolved. The solution was refluxed for ¼ hour and added with mechanical stirring in small portions to 100 cc. of water. Additions of ice kept the temperature between 35 and 50°. After hydrolysis of the phosphorus oxychloride, the mixture was cooled to 15–20° and stirred for ½ hour. The precipitated nitrile was filtered and washed, yielding a greyish-white, felt-like material (9.5 g.) beginning to melt and decompose at 300°. After two crystallizations from dioxane, the small white needles melted at 328° (block).

Anal. Calc'd for $C_{28}H_{16}N_2$: N, 7.36. Found: N, 7.20; 7.21.

9-Hydroxyfluorene-2-carboxylic acid (XIII). Fluorenone-2-carboxylic acid (3) (XII) (125 g.) was reduced with zinc dust (150 g.) activated with copper sulfate (0.5 g.) in water (2500 cc.) containing potassium hydroxide (140 g.) as described for the 1-isomer (III). The hydroxy acid does not show the tendency to produce gums as the 1-isomer does. It may be precipitated easily from alkaline solution with concentrated hydrochloric acid; yield 105 g. (84%), m.p. 237° (block). One recrystallization from ethanol raised the m.p. to 240° (block) as reported by Ray and Kreiser (21).

9-Chlorofluorene-2-carbonyl chloride (XIV). The acid (XIII) (100 g.) was refluxed with thionyl chloride (450 cc.) for one hour, yielding a brown solution. Thionyl chloride (200 cc.) was distilled off and the remaining solution allowed to stand overnight. The precipitated crystals were filtered and washed with ligroin (30–60°) until white; 63 g., m.p. 136–150°.

Anal. Calc'd for $C_{14}H_8Cl_2O$: Cl, 27.0. Found: Cl, 26.4.

The thionyl chloride filtrate was distilled to dryness on a water-bath and the residue washed with ligroin (30–60°), yielding another 45 g. of material.

Ethyl 9-chlorofluorene-2-carboxylate (XV). The crystalline acid chloride (63 g.) obtained above was refluxed with absolute ethanol (400 cc.) for one hour. The mixture was chilled and allowed to stand for two hours. The precipitated ester was filtered and washed with absolute ethanol. After air-drying, the white solid weighed 65 g. and melted at 127–128°.

The filtrate was added to the 45 g. of the less pure acid chloride. After identical treatment, a tan material (m.p. 120–125°) resulted. Recrystallized from ligroin (90–120°) (Darco) it yielded 40 g. of light tan ester, m.p. 126–128°. A sample recrystallized twice from ligroin (90–120°) melted at 128–129°.

Anal. Calc'd for $C_{16}H_{13}ClO_2$: Cl, 13.0. Found: Cl, 12.9.

Methyl 9-chlorofluorene-2-carboxylate (XVI). The acid chloride (XIV), treated with absolute methanol as described for the ethyl ester, afforded white crystals m.p. 107–109°, which when recrystallized from ligroin (60–90°) formed tiny needles, m.p. 110–111°.

Anal. Calc'd for $C_{15}H_{11}ClO_2$: Cl, 13.71. Found: Cl, 13.55.

9-Chlorofluorene-2-carboxamide (XVII). The acid chloride (XIV) (26 g.) stirred with ice-cold concentrated ammonium hydroxide (300 cc.) for one hour yielded 23.5 g. (97%) of white material, m.p. 227° dec. A sample recrystallized from isoamyl alcohol melted at 227–228° dec.

Anal. Calc'd for $C_{14}H_{10}ClNO$: N, 5.76. Found: N, 5.66.

9-Chlorofluorene-2-nitrile (XVIII). The amide (XVII) (2 g.) was treated with phosphorus oxychloride (20 cc.) as described for X. A light tan material (1.7 g.), m.p. 156–159° was obtained. When recrystallized from isoamyl alcohol (Darco), it formed small white needles, m.p. 158–159°.

Anal. Calc'd for $C_{14}H_8ClN$: N, 6.22. Found: N, 6.13.

Diethyl 9,9'-bifluoryl-2,2'-dicarboxylate (XIX). Sodium iodide (130 g.) in acetone (820 cc.) was added to ethyl 9-chlorofluorene-2-carboxylate (XV) (100 g.) in acetone (500 cc.) and the reaction carried out as for the 1,1'-isomer (VII). The yellowish white crude product (90 g.) melted with decomposition at about 200°.

Six grams of the crude material, when recrystallized three times from xylene, yielded 1.8 g. of white crystals, starting to melt partially at 220°; at 227° the melt reddens and the last crystals disappear at 245°.

Anal. Calc'd for $C_{32}H_{26}O_4$: C, 81.2; H, 5.5.
Found: C, 80.83; H, 5.49.

9,9'-Bifluoryl-2,2'-dicarboxylic acid (XX). The ester (XIX) (84 g.) was saponified with 23.6 g. of potassium hydroxide in 500 cc. ethanol as described for the 1,1'-isomer (VII), except that the acid as precipitated from the alkaline solution was digested on a steam-bath for five hours and allowed to stand overnight to facilitate filtration (the acid precipitates in very fine particles). Purification by reprecipitation from sodium hydrogen carbonate solution was omitted, except for a small amount used as an analytical sample. The acid is insoluble in the usual organic solvents; yield 72 g. (97%), m.p. >360°.

Anal. Calc'd for $C_{28}H_{18}O_4$: C, 80.5; H, 4.32.
Found: C, 79.46; H, 4.51.

9,9'-Bifluoryl-2,2'-dicarbonyl chloride (XXI). The acid (XX) (65 g.) yielded a brown solution when refluxed for six hours with thionyl chloride (600 cc.). The solution was allowed to stand overnight after distilling off 300 cc. of thionyl chloride. The resulting crystals, after filtering and washing with ligroin (30–60°) weighed 28.5 g. and melted at 284–288° dec.

Anal. Calc'd for $C_{28}H_{16}Cl_2O_2$: Cl, 15.6. Found: Cl, 14.76, 14.79.

The mother liquor distilled down to 100 cc. was diluted with 400 cc. of ligroin (30–60°), affording another 35 g. of material.

9,9'-Bifluoryl-2,2'-dicarboxamide (XXII). The acid chloride (XXI) (61 g.) was added to ice-cold concentrated ammonium hydroxide (700 cc.), stirring being maintained for one hour. After filtering and washing, 65 g. of a greyish-white material was obtained. It was very slightly soluble in hot dioxane or hot isoamyl alcohol. A sample was recrystallized from glacial acetic acid-water, yielding a white product which turns red on a copper block at 360°.

Anal. Calc'd for $C_{28}H_{20}N_2O_2$: N, 6.73. Found: N, 6.67.

An identical product was obtained as follows: A solution of sodium iodide (35 g.) in acetone (350 cc.) was added to a suspension of 9-chlorofluorene-2-carboxamide (XVII) (23 g.) in acetone (330 cc.). The mixture was refluxed on a water-bath for ½ hour, iodine being liberated. After standing for twenty-four hours, the volume was reduced to 500 cc. To the cold, brown mixture a solution of sodium hydrogen sulfite (10 g.) in water (1200 cc.) was added in portions with stirring. The light yellow suspension was stirred for ½ hour, filtered, and washed. The yellow material (20 g.), melting from 300° upward with decomposition, contained some free iodine. A small sample recrystallized from acetic acid-water, as before, gave the white amide.

9,9′-Bifluoryl-2,2′-dinitrile (XXIII). The amide (XXII) (65 g.) was treated with phosphorus oxychloride (200 cc.) as described for the 1,1′-isomer (XI). A crude yield of 62 g. of grey-tan material, shrinking around 90° and forming a pasty brown mass from 110° upward, was obtained. *Separation of isomers.* The crude material was dissolved in 300 cc. of acetone, boiled with Darco for ½ hour, and filtered. The filtrate was reduced to 200 cc. and allowed to stand overnight. After filtering off the crystals and washing with five 20-cc. portions of acetone, a second crop was obtained by evaporating the mother liquor to 100 cc. The two solid fractions were combined (21.8 g.) and extracted with a limited amount of acetone (125 cc.), affording 12 g. of a granular white material (A), m.p. 215–235°. The combined acetone mother liquors were evaporated. The resulting dark oil was refluxed with 300 cc. of isoamyl alcohol, clarified with Darco, and cooled to allow crystallization. After filtration and evaporation of the filtrate, a total amount of 24.5 g. of material (B), m.p. 110–140° was obtained.

After ageing for four weeks, a sample of material (A) recrystallized three times from isoamyl alcohol formed beautiful white needles, m.p. 264–267° dec.

Anal. Calc'd for $C_{28}H_{16}N_2$: N, 7.36. Found: N, 7.39, 7.44.

A sample of material (B) recrystallized twice from isoamyl alcohol formed light tan granular crystals, m.p. 110–135° dec.

Anal. Calc'd for $C_{28}H_{16}N_2$: N, 7.36. Found: N, 7.20.

Diethyl 9,9′-bifluoryl-2,2′-dicarbimidate dihydrochloride (XXIV). 9,9′-Bifluoryl-2,2′-dinitrile (XXIII) (6 g.) was dissolved in absolute dioxane (50 cc.). Absolute ethanol (5 cc.) was added and the solution cooled in an ice-salt bath. Dry hydrogen chloride was bubbled in until the solution was saturated. The flask was stoppered and allowed to stand at room temperature for twenty-eight hours. The resulting crystals were filtered and washed with peroxide-free anhydrous ether. The white material melted on a copper block with decomposition around 215°. In a capillary only a progressive shrinking was noted from 180° upwards (decomposition into amide and ethyl chloride).

Anal. Calc'd for $C_{32}H_{30}Cl_2N_2O_2$: N, 5.13. Found: N, 4.75.

An additional amount was recovered by diluting the filtrate with 150 cc. of anhydrous ether.

9,9′-Bifluoryl-2,2′-dicarboxamidine dihydrochloride (XXV). Absolute ethanol (150 cc.) saturated at 0° with ammonia was added to the imido ester (XXIV). A light yellow solution was formed after standing for sixty hours. It was filtered and reduced *in vacuo* to 50 cc. The white crystalline precipitate thus formed was filtered, washed with small amounts of absolute ethanol and ether and dried in a vacuum desiccator. It weighed 4.0 g. The filtrate was reduced to 20 cc. and diluted with 100 cc. of peroxide-free ether. The precipitate was filtered and washed with ether, taking care to keep the solid covered with liquid. The ether was allowed to evaporate slowly in a large desiccator, leaving 2.9 g. of cream-white, soft material. The total yield was 6.9 g. or 90%. The salt is freely soluble in water or 95% ethanol. The finely divided material was very sensitive to air oxidation. Moisture and ether peroxides probably catalyzed the oxidation. In one run, where no particular precautions were taken, the white 9,9′-bifluoryl derivative was oxidized quantitatively to the red 9,9′-bifluorylidene. Crystallization from 6 *N* hydrochloric acid also yielded the bifluorylidene. Crystallization in the presence of zinc dust prevented the oxidation.

A sample recrystallized from absolute ethanol-ether shrank around 270°, deepening in color from white to orange to red and finally starting to melt at 310°.

Anal. Calc'd for $C_{28}H_{24}Cl_2N_4$: N, 11.50. Found: N, 11.32, 11.13.

SUMMARY

In the search for substances of possible physiological activity, a number of symmetrically disubstituted derivatives of 9,9′-bifluoryl have been prepared. These include 9,9′-bifluoryl-1,1′-dinitrile and intermediates, and 9,9′-bifluoryl-2,2′-dicarboxamidine dihydrochloride and intermediates.

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