i-**Cholesteryl Methyl Ether** (VIII).—The above sirup was dissolved in 60 ml. of absolute ethanol, 300 mg. of platinum oxide added and the hydrogenation carried out at atmospheric pressure. After 78% of the theoretical amount of hydrogen had been taken up, the reaction stopped and a small amount of white solid began to precipitate. The solution was warmed, filtered and concentrated to 15 ml. The solid product weighed 1.9 g. (61%) and melts at 73.0–74.5° and shows no depression on admixture with an authentic sample.

Cholesterol (IX).—The *i*-ether (VIII, 0.5 g., 1.20 mmoles) was converted to cholesterol following the procedure of McKennis.[7] Recrystallization from methanol yielded 0.42 g. (87%) of plates, m. p. 145.0–146.0°.

25-Acetoxycholesteryl Acetate (IV).—A solution of 0.20 g. (0.49 mmole) of the diol (II) in 10 ml. of acetic anhydride and 2 drops of pyridine was refluxed for one hour, cooled and poured into 250 ml. of cold water. The mixture was allowed to stand for several hours with occasional swirling until the product solidified. The solid was filtered and dried to give a quantitative yield of the crude diacetate which was recrystallized from methanol to give 0.17 g. (72%) of plates, m. p. 119.0–120.5°. $[\alpha]^{25}_D$ −35.5° (chloroform).

Anal. Calcd. for $C_{31}H_{50}O_4$: C, 76.50; H, 10.35. Found: C, 76.96; H, 10.40.

Conversion of IV to Dehydrocholesterol (VI).—The crude diacetate obtained by acetylating 0.50 g. (1.25 mmoles) of diol under the above conditions was refluxed for five hours with 25 ml. of dry benzene and 3 ml. of phosphorus tribromide, poured into ice and ether and the extract washed, dried and concentrated as described above. The residual material was refluxed with 5 ml. of collidine for three hours and processed as in the conversion of III to V. The solid residue was directly hydrolyzed by refluxing in 50 ml. of 5% ethanolic potassium hydroxide for two hours. The solution was concentrated, diluted with water, cooled and filtered to give 0.33 g. of crystals, m. p. 104–106°. After two further recrystallizations from ethanol 0.29 g. (60% over-all) of beautiful plates were obtained, m. p. 117–119°, undepressed upon admixture with an authentic sample.

The diacetate is not converted to the dehydro-ester by thermal cleavage in hot collidine and is recovered unchanged after refluxing in collidine solution for four hours.

The diacetate is converted, however, to the bromo compound by the action of phosphorus tribromide. A solution of 0.35 g. (0.79 mmole) of the diacetate in 20 ml. of dry benzene and 2 ml. of phosphorus tribromide was refluxed for five hours and then processed as described above. The twice recrystallized product, m. p. 114–116°, weighed 0.23 g. (58%). A mixed melting point between this product and the bromo compound previously obtained showed no depression. The compound also sublimed in the same characteristic slow fashion to give dehydrocholesteryl acetate, m. p. 85–89°, in good agreement with the value obtained for the sublimate from the first bromo compound. One recrystallization from methanol raised the m. p. to 89.5–90.5°. The diacetate, itself, sublimes without decomposition.

Infrared Spectra.—All spectra were taken in carbon disulfide solution using a narrow sodium chloride cell.

Summary

1. A procedure has been developed for the synthesis of cholesterol from Δ^5-norcholestene-3β-ol-25-one in 28.5% yield.

2. Norcholestenol-25-one was allowed to react with methylmagnesium iodide to give 25-hydroxycholesterol, which in turn was converted to the monoacetate. The monoacetate was dehydrated by the action of phosphorus tribromide and collidine to give Δ^{25}-dehydrocholesteryl acetate. The ester was hydrolyzed to the free sterol which was then converted to *i*-dehydrocholesteryl methyl ether. The *i*-ether was hydrogenated over platinum oxide to give *i*-cholesteryl methyl ether which was subsequently hydrolyzed to cholesterol.

BERKELEY 4, CALIF. RECEIVED APRIL 3, 1950

[CONTRIBUTION FROM THE LABORATORY OF RADIOCHEMISTRY, UNIVERSITY OF CINCINNATI]

The Structure of Fluorene[1]

BY JOHN H. WEISBURGER,[2] ELIZABETH K. WEISBURGER AND FRANCIS EARL RAY

Although the structure of fluorene would appear to be straightforward, there have been a number of conflicting opinions with regard to the spatial configuration of this hydrocarbon.

Cook and Iball[3] proposed a folded ring structure with the planes of the six-membered rings inclined at an angle of 20° to the plane of the five-membered ring. On the other hand Pinck and Hilbert[4] favor a uniplanar model.

A preliminary consideration of resonance energy, bond lengths, bond angles and absorption spectra provides evidence for one form.

According to theoretical organic chemistry resonance could occur throughout a planar structure but would be limited to the benzene rings in a folded fluorene molecule. The resonance energy given in the literature[5] for fluorene is appreciably higher (101 kcal./mole) than that corresponding to two benzene rings (82 kcal./mole) alone.

Moreover, from the bond lengths[4,6] in the five-membered ring, the partial double bond character of these bonds may be calculated with the following results: The bond joining the benzene rings has a 12.5% double bond character (like biphenyl), the bonds between the benzene rings and the 9 carbon a 15% and the bonds in the benzene rings a 37% double bond character. This could be interpreted as indicating that resonance takes place throughout the entire molecule.

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[1] This work was supported by grant N7-onr-479 from the Office of Naval Research. Presented at the meeting of the Ohio Academy of Science, Granville, Ohio, April, 1949. A portion of the thesis submitted to the Graduate School, University of Cincinnati, by John H. Weisburger in partial fulfillment of the requirements for the degree of Doctor of Philosophy, June, 1949.

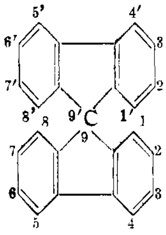
[2] National Cancer Institute, Bethesda 14, Maryland.

[3] Cook and Iball, *Chem. and Ind.*, **55**, 467 (1936).

[4] Pinck and Hilbert, THIS JOURNAL, **59**, 8 (1937).

[5] Wheland, "Theory of Resonance," John Wiley & Sons, Inc., New York, N. Y., 1944, p. 69.

[6] Iball, *Z. Krist.*, **94**, 397 (1936).



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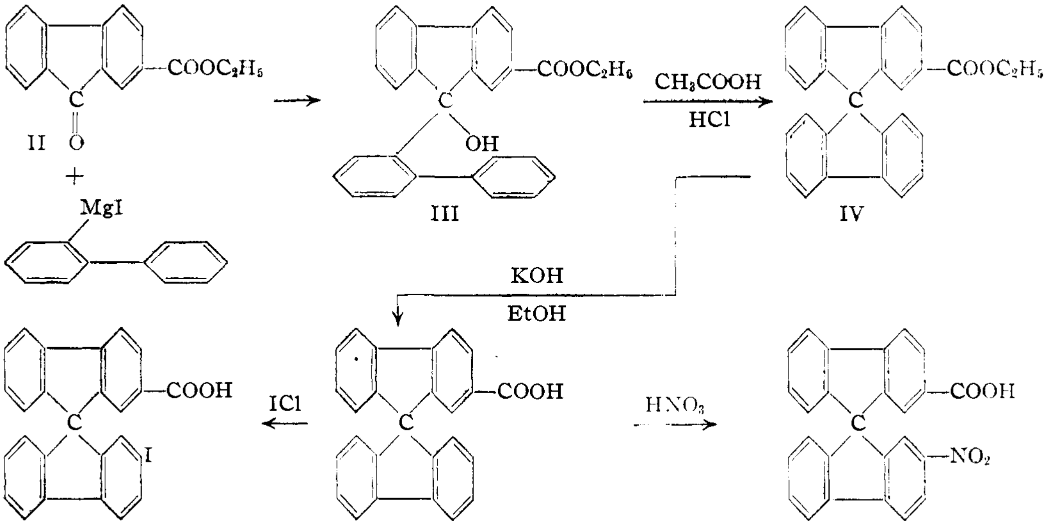

II III IV VI V VII

Pinck and Hilbert attributed considerable strain to the planar structure, whereas Cook and Iball thought the folded model to be strainless. Various ring enlargements or contractions were inconclusive with regard to the configuration.[4] On the other hand a discussion in Gilman[7] leads to the conclusion that the molecule would be strainless if the bonds were fixed as in the Mills–Nixon effect. It was shown, however, that such an effect does not prevail in fluorene.[8,9] Pinck and Hilbert's claim for considerable strain in fluorene is disproved by the same argument, since their calculations are based on a single, fixed-bond structure. The solution must be an intermediate structure, composite of all resonance hybrids, endowed with a small amount of strain.

This slight strain causes the fine structure effect in the absorption spectrum of fluorene.[10] The relationship between the spectrum and planarity of a molecule was investigated by O'Shaughnessy and Rodebush[11] in a series of substituted biphenyls. The absorption spectrum of fluorene[10,12] is strikingly similar to that of the unsubstituted, planar biphenyl, except for a shift to a longer wave length attributable to the higher resonance energy of fluorene. Thus the interpretation of physical data favors the planar structure of fluorene.

The recent resolution of 9,2-substituted fluorenes[13] suggested a further experimental study of the structure of fluorene by means of stereochemical methods.

9,9′-Spirobifluorene (I) was synthesized by Clarkson and Gomberg.[14] If this spirane is monosubstituted, models show that two resolvable racemates (four enantiomorphs) exist in a folded structure. Only one compound can be constructed if fluorene is planar. Thus the resolution or non-resolution of a monosubstituted 9,9′-spirobifluorene affords experimental evidence regarding the structure of fluorene. A properly disubstituted spirane should be resolvable irrespective of the configuration of fluorene. Therefore the preparation and resolution of a disubstituted 9,9′-spirobifluorene was undertaken first. The spirane derivatives were prepared by a modification of Clarkson and Gomberg's procedure. The 2-carbethoxyfluorenone (II) reacted with 2-biphenylmagnesium iodide to yield 2-carbethoxy-9-(2-biphenyl)-9-fluorenol (III). Ring closure on the latter compound produced 2-carbethoxy-9,9′-spirobifluorene (IV) which on saponification afforded the spiranecarboxylic acid (V).

Iodination of the spiranecarboxylic acid with iodine monochloride resulted in a theoretical

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(7) Gilman, "Organic Chemistry," John Wiley and Sons, Inc., New York, N. Y., 1947, p. 136.

(8) Lothrop, THIS JOURNAL, **61**, 2115 (1939).

(9) Bergmann and Berlin, *ibid.*, **62**, 316 (1940).

(10) Jones, *ibid.*, **67**, 2131 (1945).

(11) O'Shaughnessy and Rodebush, *ibid.*, **62**, 2906 (1940).

(12) Ramart-Lucas and Hoch, *Bull. soc. chim.*, [5] **2**, 1376 (1935).

(13) Ray and Kreiser, THIS JOURNAL, **69**, 3068 (1947).

(14) Clarkson and Gomberg, *ibid.*, **52**, 2881 (1930).

increase in weight. The crude product could be purified only with difficulty because the impurity and by-products concentrated during the process, while the desired acid remained in the mother liquors.

The 2′-iodo-9,9′-spirobifluorene-2-carboxylic acid was resolved using strychnine. No clear-cut separation into two fractions of diastereoisomeric salts occurred. Numerous small fractions were obtained. Upon systematic recrystallization and decomposition they yielded optically active acids. Hence, it was shown that a disubstituted spirobifluorene was resolvable.

The crucial compound, however, was the monosubstituted spirane carboxylic acid. This formed a nicely crystalline salt with strychnine. Four fractions of the salt isolated had the same melting point and an identical specific rotation. After decomposition it afforded fractions of the acid that were optically inactive.

The failure to resolve this monosubstituted spirobifluorene supports the evidence mentioned earlier that fluorene is planar.

Experimental

2-Carbethoxyfluorenone (II).—Seventy-five grams of fluorenone-2-carboxylic acid[15] was refluxed with 800 ml. of thionyl chloride for four hours. After distilling off the excess thionyl chloride, 200 ml. of absolute ethanol was added and the mixture digested on a steam-bath for 0.5 hour. Addition of 250 ml. of dry benzene caused the ester to go into solution. The solution was filtered and 100 ml. of solvent distilled off. On cooling 69.0 g. of product, m. p. 139–143°, crystallized. Recrystallization using Darco afforded 59.4 g. of long lemon colored needles, m. p. 140–142.5°. *Anal.* Calcd. for $C_{16}H_{12}O_3$: C, 76.11; H, 4.77. Found: C, 76.52; H, 4.91.

2-Carbethoxy-9-(2-biphenyl)-9-fluorenol (III).—A Grignard reagent was prepared from 36 ml. of 2-iodobiphenyl dissolved in 80 ml. of anhydrous ether and 5.0 g. of magnesium covered with 80 ml. of ether. After reacting for 1.5 hours the solution was decanted into a separatory funnel and diluted with 200 ml. of ether. This Grignard was dropped with mechanical stirring into a refluxing solution of 50 g. of 2-carbethoxyfluorenone in 225 ml. of anhydrous benzene over a period of 75 minutes. The yellow suspension was stirred and refluxed for another three hours, then cooled and filtered. The solid was washed well with ether and air-dried for a short time. The powdery yellow addition complex was decomposed by stirring for two hours with 1 l. of 10% ammonium chloride solution. After filtering and drying the crude product weighed 74.2 g. and melted between 155 and 165°. It was recrystallized by dissolving in 700 ml. of hot benzene, treating with Darco, and adding rapidly 1500 ml. of ligroin (30–60°) in one portion to the hot benzene solution. After standing for two hours in an ice-bath 64.4 g. of nearly colorless plates, m. p. 189–192.5°, was obtained. The analytical sample was crystallized twice more to yield brilliant white plates, m. p. 193–194.5°. *Anal.* Calcd. for $C_{28}H_{22}O_3$: C, 82.73; H, 5.42. Found: C, 83.01; H, 5.30.

2-Carbethoxy-9,9′-spirobifluorene (IV).—Sixty grams of III was dissolved in 350 ml. of hot glacial acetic acid. At the boiling point a few drops of concentrated hydrochloric acid was added through the condenser. The reaction took place rapidly, as evidenced by the evolution of heat. After five minutes, Darco was added and the mixture refluxed for fifteen minutes. After filtration, the clear solution was added with mechanical stirring to 2 l. of ice-water, giving a fluffy white precipitate. The air-dried powder weighed 54.7 g., m. p. 80–100°. A sample (1.0 g.) was successively recrystallized from ligroin and ethanol to yield shiny white prismatic plates (0.7 g.), m. p. 174–177°. *Anal.* Calcd. for $C_{23}H_{20}O_2$: C, 86.57; H, 5.16. Found: C, 86.34; H, 5.01.

9,9′-Spirobifluorene-2-carboxylic Acid (V).—A portion of the crude 2-carbethoxy-9,9′-spirobifluorene (25.8 g.) was saponified with 250 ml. of 10% alcoholic potassium hydroxide in a period of 45 minutes. Hot water (200 ml.) and Darco were added, the mixture refluxed for five minutes and filtered hot. More hot water (500 ml.) was added and the solution acidified at the boiling point with good stirring. The heavy white precipitate was stirred another 15 minutes, filtered and washed well. The product weighed 22.3 g. and melted at 350° (block). Recrystallization from 2300 ml. of acetic acid produced 18.3 g. of shiny white needles, m. p. 356° (block). *Anal.* Calcd. for $C_{26}H_{16}O_2$: C, 86.64; H, 4.44. Found: C, 86.88; H, 4.41.

Attempts at Resolution of 9,9′-Spirobifluorene-2-carboxylic Acid (V).—Three and five-tenths grams of V was suspended in 100 ml. of hot acetone. A hot solution of 3.3 g. of strychnine in 45 ml. of chloroform was added. The resulting solution was filtered hot and the solvents removed *in vacuo*. Addition of 210 ml. of absolute ethanol and refluxing for several hours caused most of the salt to dissolve. The solution was filtered hot and allowed to stand for four days. Fraction I in the form of short stubby needles, assembled in rosettes, weighing 5.4 g. and melting at 240° was obtained. In two steps the filtrate was reduced to dryness giving Fractions II and III of identical aspect weighing 0.6 and 0.7 g., respectively. Systematic crystallization produced five fractions: Ia (4.3 g., m. p. 239–240°, $[\alpha]^{28}\text{D}$ −37.2°, $C = 0.4044$). *Anal.* Calcd. for $C_{47}H_{38}O_4N_2 \cdot C_2H_5OH$: C, 79.43; H, 5.95; N, 3.79. Found: C, 79.20; H, 5.70; N, 3.80. IIa (1.3 g., m. p. 238–240°, $[\alpha]^{28}\text{D}$ −37.0°, $c = 0.5005$); IIIa (0.2 g., m. p. 236–239°, $[\alpha]^{28}\text{D}$ −36.4°, $c = 0.4980$); IVa (0.2 g., m. p. 233–236°, $[\alpha]^{28}\text{D}$ −31.4°, $c = 0.4780$); Va (0.2 g., m. p. 220°, $[\alpha]^{28}\text{D}$ −25.4°, $c = 0.5545$). The last two small fractions were combined and recrystallized once more to give fraction IVa′ (0.2 g., m. p. 238–240°, $[\alpha]^{28}\text{D}$ −38.4°, $c = 0.2935$). The salts were decomposed by solution in acetone, acidification and addition of hot water. The solutions of the resulting acids in acetone were optically inactive. After recrystallization from acetic acid, the melting point was unchanged at 356°, *i. e.*, identical with that of the starting material.

2′-Iodo-9,9′-spirobifluorene-2-carboxylic Acid (VI).—Twelve grams of V were dissolved in 1350 ml. of hot acetic acid. Iodine monochloride (15 ml.) followed by 20 ml. of acetic anhydride was added and the mixture refluxed for six hours. The solvent and excess iodine monochloride were distilled off to about 300 ml. and the mixture cooled. The resulting white crystals were filtered and washed with acetic acid. They weighed 12.2 g. Dilution of the filtrate at the boiling point with water containing some sodium bisulfite afforded another 4.6 g. The combined fractions were dissolved in 1 l. of hot acetic acid, treated with Darco, and 600 ml. of solvent distilled off. Upon cooling, 10.0 g. of material, m. p. 345°, crystallized. Part of this product was used in the resolution to be described later. An analytical sample (1.5 g.) was recrystallized twice from acetic acid and four times from chloroform, yielding 0.3 g. of white microneedles, m. p. 349–351°. *Anal.*[16] Calcd. for $C_{26}H_{15}O_2I$: C, 64.21; H, 3.11. Found: C, 63.81; H, 3.53.

Resolution of 2′-Iodo-9,9′-spirobifluorene-2-carboxylic Acid (VI).—Four and eight-tenths grams of VI and 3.3 g. of strychnine were suspended in 200 ml. of ethanol and the mixture refluxed for 1.5 hours. The resulting solution was filtered hot, reheated and allowed to stand overnight in a refrigerator. A cream colored powder weighing 1.3 g. (fraction 1) was obtained. Successive reductions of the

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(15) Rieveschl and Ray, "Organic Syntheses," **28**, 63 (1948).

(16) The authors are indebted to M. Jensen and R. Koegel, National Cancer Institute, for this analysis.

volume yielded five further fractions weighing 2.0, 1.7, 0.9, 1.4 and 0.9 g. Systematic recrystallization of these fractions afforded eight fractions. Their weights and specific rotations in acetone are given in Table I.

TABLE I

RESOLUTION OF 2′-IODO-9,9′-SPIROBIFLUORENE-2-CARBOXYLIC ACID WITH STRYCHNINE

Fract. of salt	Salt, g.	Spec. rot.	Acid, g.	M. p., °C.	Rotation Actual	Rotation Specific
1	0.4	−26.6	0.25	318	−0.06	− 7.1
2	1.3	−26.7	0.8	328	− .05	− 5.1
3	0.6	−28.1	0.4	336	− .03	− 3.2
4	0.8	−31.6	0.5	341	+ .15	+15.5
5	0.6	−18.6	0.35	350	+ .28	+25.5
6	0.3	−39.8	0.2	336	− .02	− 2.0
7	0.8	−27.2	0.5	347	+ .12	+15.0
8	2.1	−51.9	1.0	344	− .18	−16.8

The various fractions of salt were decomposed by solution in a small volume of acetone, acidification and dilution with hot water. The resulting precipitates were filtered, washed with hot water and air-dried. The results are shown in Table I. The fractions of maximum positive and negative rotations were recrystallized from acetic acid. Fraction 5 yielded 0.1 g. (m. p. 350–351°; α +0.10°, $[\alpha]^{28}\mathrm{D}$ +16.9°) from 20 ml. of solvent. The filtrate diluted with 5 ml. of water at the boiling point gave 0.2 g. (m. p. 350–351°, α +0.19°, $[\alpha]^{28}\mathrm{D}$ +37.9°). Fraction 8 from 55 ml. of solvent yielded 0.5 g. (m. p. 344–345°, α −0.09°, $[\alpha]^{28}\mathrm{D}$ −14.3°). The filtrate diluted with 18 ml. of water produced 0.4 g. (m. p. 341–342°, α −0.11°, $[\alpha]^{28}\mathrm{D}$ −16.8°).

2′-Nitro-9,9′-spirobifluorene-2-carboxylic Acid (VII).—Fourteen and seven-tenths grams of V was dissolved in 1300 ml. of hot acetic acid. With mechanical stirring 370 ml. of concentrated nitric acid (d. 1.42) was run into the boiling solution over a period of 25 minutes. Toward the end a precipitate started forming. The mixture was refluxed with stirring for another 70 minutes and allowed to stand for four hours. The yellow microcrystals were filtered off, washed with acetic acid and alcohol, and oven-dried. They weighed 10.3 g. After recrystallization from 220 ml. of nitrobenzene, 9.3 g. of small granules, m. p. 360°, was obtained. *Anal.* Calcd. for $C_{26}H_{15}O_4N$: N, 3.46. Found: N, 3.41. From the acetic acid filtrate a further 5.8 g. of crude material was recovered by dilution with water.

Summary

On the basis of theoretical considerations fluorene was shown to be planar. This finding was corroborated experimentally by a study of the stereochemistry of mono- and disubstituted 9,9′-spirobifluorenes.

CINCINNATI 21, OHIO

RECEIVED MAY 23, 1949

[CONTRIBUTION FROM THE LABORATORY OF RADIOCHEMISTRY, UNIVERSITY OF CINCINNATI]

Some Derivatives of 9,9′-Spirobifluorene[1]

BY JOHN H. WEISBURGER,[2] ELIZABETH K. WEISBURGER[2] AND FRANCIS E. RAY[3]

The chemistry of 9,9′-spirobifluorene, first synthesized by Clarkson and Gomberg,[4] was investigated in connection with a study of the structure of fluorene.[5]

With concentrated sulfuric acid sulfonation of 9,9′-spirobifluorene did not occur below 100° while above this temperature disulfonation resulted. When one equivalent of chlorosulfonic acid in chloroform was employed about one-half of the spirane disulfonated; the remainder was recovered unchanged.

This tendency for disubstitution was also observed in the nitration of 9,9′-spirobifluorene. However, by rather careful control of the concentration of nitric acid and the reaction time, it was eventually possible to isolate a small amount of the pure monosubstituted derivative.

It is not surprising that the spirane disubstitutes readily if its structure is considered in detail. The absorption spectrum shown in Fig. 1 closely resembles the sum of the spectra of fluorene and biphenyl.[6] This indicates negligible resonance coupling[6,7] between the two moieties of 9,9′-spirobifluorene with the result that each spirane molecule acts as if it consisted of two nearly independent fluorene molecules. The isolation of a monosubstituted spirobifluorene appears possible only if there is an appreciable difference in the energy of activation of the mono- and disubstitution reactions.

Considering the close relationship of 9,9′-spirobifluorene to fluorene, it seemed likely that electrophilic substituents would attack the 2 position. This was confirmed by degrading the known 9,9′-spirobifluorene-2-carboxylic acid[5] to the amine by a Curtius reaction. This amine was identical with the amine obtained by nitration of the hydrocarbon and reduction of the nitro derivative. In disubstitution one group would be expected to enter into each moiety of the hydrocarbon. This indeed takes place since the 2-iodo-9,9′-spirobifluorene-2′-carboxylic acid[5] and the 9,9′-spirobifluorene-2,2′-disulfonic acid[8] were found to be resolvable. If both groups were located in the same moiety of the spirane, these compounds would not be resolvable. The 9,9′-spirobifluorene derivatives prepared during this investigation are shown in Table I.

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(2) Biochemistry Section, National Cancer Institute, Bethesda 14, Maryland.

(3) Cancer Research Laboratory, University of Florida, Gainesville, Florida.

(4) Clarkson and Gomberg, THIS JOURNAL, **52**, 2881 (1930).

(5) Weisburger, Weisburger and Ray, *ibid.*, **72**, 4250 (1950).

(6) Jones, *ibid.*, **67**, 2021, 2127 (1945).

(7) Branch and Calvin, "Theory of Organic Chemistry," Prentice-Hall, Inc., New York, N. Y., 1941, pp. 168 ff.

(8) J. H. Weisburger, Ph.D. Thesis, University of Cincinnati, 1949, p. 61.