are compared with the products from the corresponding Grignard reagent. Instead of the products of secondary addition observed with the Grignard reagent,[3] mixtures were obtained, the composition depending on the carbonyl compound employed.

The composition of the reaction mixture is a direct measure of the ratio of the rates of formation of products at the primary and the secondary carbon atoms of the allylic carbanion, K_p/K_s. For carbon dioxide, this ratio is about 0.1, phenylvinylacetic acid being formed about ten times as rapidly as β-benzalpropionic acid. For acetone the ratio is about 0.5, and for benzophenone, the ratio is quite large, since only one addition product could be isolated.

Nothing can be said about the absolute values of K_p and K_s, however, among the factors which could affect these constants and their ratio, steric effects probably play a prominent role.

Summary

1. The reactions of sodium allylbenzene with carbon dioxide, acetone, and benzophenone have been studied.

2. The reaction products are different from those obtained in similar reactions of allylic Grignard reagents, in that mixtures are produced which depend on the nature of the carbonyl group, while the Grignard reagent in all cases gives only one product, that of secondary addition.

3. It is considered that these mixtures arise due to different rates of reaction at the primary and the secondary carbon atom of the allylbenzene carbanion.

LOS ANGELES, CALIFORNIA RECEIVED APRIL 21, 1947

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

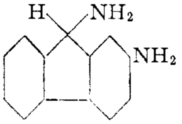
The Resolution of 9,2-Substituted Fluorenes[1]

BY FRANCIS EARL RAY AND ELIZABETH KREISER[2,3]

According to present-day theories there are two structures which may be assigned to fluorene. One is a uniplanar structure,[4] the other is 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.[5] If this latter be the case, substitution of the 9-carbon atom can produce two possible isomers, depending on whether the substituent group is *cis* or *trans* to the inclined six-membered rings.

The previous attempts to prove that fluorene possessed a non-planar structure by isolation of *cis–trans* isomers were unsuccessful.[6] Resolution of a fluorene substituted only on the 9-carbon would also be conclusive evidence for a non-planar form.

Bader[7] attempted to resolve the classically asymmetric 2,9-diaminofluorene, I, with *d*-tartaric acid and also by the aldehyde condensation with *d*-helicin and failed. He explained his failure by a novel theory that optical isomers do not exist in this case because of a mutual repulsion between the two amino groups that destroys the tetrahedral arrangement of the 9-carbon atom by forcing the substituents on the 9-carbon into the same plane.



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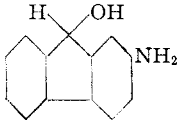

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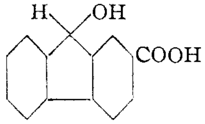

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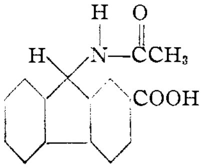

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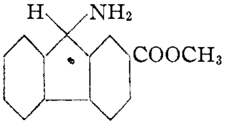

V

Later Bennett and Noyes[8] attempted to resolve 2,9-diaminofluorene using *d*-camphorsulfonic acid, *d*-phenylaminoacetic acid and *d*-hydroxymethylene camphor. These attempts, as well as an attempt to resolve 2-amino-9-hydroxyfluorene, II, with *d*-camphorsulfonic acid, were unsuccessful. Their opinion was that failure to resolve these compounds was caused by lack of the proper experimental conditions rather than any inherent symmetry. They, nevertheless, point out that Billon[9] was unable to resolve analogous compounds of the type $ArCHNH_2Ar'$.

It is of considerable importance that the possibility of resolving compounds with a 9-asymmetric carbon be thoroughly explored because if

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[1] Reported at the Chicago meeting of the American Chemical Society, September, 1946.

[2] Sloan-Kettering Institute for Cancer Research Fellow 1946–1947.

[3] A portion of the thesis submitted to the Graduate School, University of Cincinnati, by Elizabeth Kreiser in partial fulfillment of the requirements for the degree of Doctor of Philosophy, June, 1947.

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

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

[6] Kliegl, Weng and Wiest, *Ber.*, **63**, 1262, 1631 (1930).

[7] Bader, Thesis, Ludwig Maximilian University of Munich, 1926.

[8] Bennett and Noyes, THIS JOURNAL, **52**, 3437 (1930).

[9] Billon, *Ann. chim. phys.*, [10] **7**, 314, 384 (1927).

it is impossible to resolve such compounds, there is even less hope of being able to isolate optical isomers which might exist because of a folded structure.

We therefore prepared 9-hydroxyfluorene-2-carboxylic acid,[10] III, avoiding the amino compounds with which the previous investigators had worked, and effected its resolution with strychnine, Table I. This was reported in 1945.[11]

TABLE I

9-HYDROXYFLUORENE-2-CARBOXYLIC ACID

Actual and Specific Rotations of Isomers

Wave length of light, Å.	Actual rotation		Specific rotation	
	Dextro[a]	Levo[a]	Dextro	Levo
6563	α^{27} +0.82°	α^{27} −0.83°	$[\alpha]^{27}$ +29.3°	$[\alpha]^{27}$ −27.6°
5893	α^{27} +1.11°	α^{27} −1.09°	$[\alpha]^{27}$ +39.6°	$[\alpha]^{27}$ −36.3°
5463	α^{27} +1.39°	α^{27} −1.35°	$[\alpha]^{27}$ +49.6°	$[\alpha]^{27}$ −45.0°

[a] The actual rotation for the dextro compound was found using 0.7000 g. of the acid in 50 cc. of ethanol in a 2-dm. tube. The actual rotation for the *levo* compound was found using 0.7500 g. of the acid in 50 cc. of ethanol in a 2-dm. tube.

TABLE II

METHYL 9-AMINOFLUORENE-2-CARBOXYLATE: ROTATIONS FROM VARIOUS FRACTIONS OF TARTRATE SALT

Wave length of light, Å.	First fraction 0.3000 g. in 50 ml. ethanol		Second fraction 0.2000 g. in 50 ml. ethanol		Third fraction 0.1500 g. in 50 ml. ethanol	
	Act. rotn.[a]	Sp. rotn.	Act. rotn.	Sp. rotn.	Act. rotn.	Sp. rotn.
6563	−0.08°	$[\alpha]^{27}$ +6.7°	+0.02°	$[\alpha]^{27}$ +3.75°	−0.03°	$[\alpha]^{27}$ − 5.0°
5893	− .09°	$[\alpha]^{27}$ +7.5°	+ .08°	$[\alpha]^{27}$ +10.0°	− .07°	$[\alpha]^{27}$ −11.7°
5463	− .11°	$[\alpha]^{27}$ +9.2°	+ .13°	$[\alpha]^{27}$ +16.3°	− .09°	$[\alpha]^{27}$ −15.0°

[a] The actual rotations were found using a 2-dm. tube.

The resolution of this compound[11] increased the hope of being able to resolve an aminofluorene compound. An attempt, accordingly, was made to resolve 9-acetylaminofluorene-2-carboxylic acid, IV, with both strychnine and brucine. The free acid instead of the diastereoisomeric salt came out of solution, and no resolution resulted.

Since resolution by salt formation with the carboxyl group had failed, recourse was had to the amino group. As the amino group is directly attached to the asymmetric carbon, its combination with an optically active acid might prevent racemization once resolution had been achieved.

The methyl ester of fluorenone-2-carboxylic acid[12] was converted into the oxime, which was reduced, producing the hydrochloride of methyl 9-aminofluorene-2-carboxylate. An attempt to resolve this compound by use of the silver salt of *d*-camphorsulfonic acid was unsuccessful.

From molecular quantities of the amine, V, and *d*-tartaric acid three fractions of crystalline material were obtained. From the first fraction, the dextro form of the amine was obtained. The second fraction also yielded the dextro form but with generally enhanced rotation. The third fraction gave the levo form.

The free, optically active amines racemized readily, even on standing at room temperature. Recrystallization was impossible without loss of activity. To determine the rotations, therefore, it was necessary to wash the free amine well, dry quickly, and dissolve without warming the solvent. The rotations obtained are shown in Table II.

The ready racemization of this amine may explain why previous attempts to resolve aminofluorenes were not successful. It may also be interpreted as bearing out Cook and Iball's theory that the non-planar fluorene molecule oscillates rapidly between two non-planar forms.

On the other hand, the ready racemization of the compounds may have been catalyzed by the presence of impurities.

Experimental

9-Hydroxyfluorene-2-carboxylic Acid.—Seventy grams of fluorenone-2-carboxylic acid (0.312 mole),[10] 240 g. (3.67 mole) of zinc dust, and 1500 cc. of ethanol were mixed in a flask equipped with a reflux condenser and ammonia trap. Then 400 cc. of concentrated ammonium hydroxide was added and the mixture refluxed. Subsequent portions of 100 and 150 cc. of ammonium hydroxide were added after one and three hours of refluxing, respectively. The total time of refluxing was five hours. The hot mixture was filtered and the filtrate poured with stirring into 8 liters of water containing 600 cc. of concentrated hydrochloric acid. The 9-hydroxyfluorene-2-carboxylic acid precipitated as a fluffy white material which was filtered and washed with water. After recrystallization from ethanol, the creamy-white needles melted at 240° (block) and weighed 39 g. or 55%.

Anal. Calcd. for $C_{14}H_{10}O_3$: C, 74.3; H, 4.46; neut. equiv., 226. Found: C, 74.3; H, 4.58; neut. equiv., 226.

Resolution of 9-Hydroxyfluorene-2-carboxylic Acid.—To 11.3 g. (0.05 mole) of 9-hydroxyfluorene-2-carboxylic acid in 125 cc. of 95% ethanol there was added 16.7 g. (0.05 mole) of strychnine in 125 cc. of chloroform. Distillation removed the greater part of the chloroform. The next day, crystals in the form of rosets, weighing 13.2 g., were obtained. These, recrystallized from 700 cc. of ethanol, sintered at 190° and melted at 203°. This strychnine salt was dissolved in a mixture of 100 cc. of ethanol and 100 cc. of 2% sodium hydroxide. This was poured into a liter of water containing 20 cc. of 6 *N* hydrochloric acid. The white fluffy precipitate was recrystallized from 60 cc. of ethanol and fine needles melting at 263° (block) were obtained. The rotations obtained are shown in Table I.

The mother liquor from the precipitation of the insoluble *d*-acid salt was boiled with Darco and filtered. The levo acid was isolated from this solution similarly to the dextro form and recrystallized from 75 cc. of ethanol. The acid had a light yellow color which a second recrystallization did not remove. The purified acid melted at 260° (block).

Preparation of Oxime of Fluorenone-2-carboxylic Acid.—To a mixture of 50 g. (0.223 mole) of fluorenone-2-carboxylic acid and 50 g. (0.595 mole) of sodium acid carbonate in 750 cc. of 50% ethanol there was added 25 g. (0.36 mole) of hydroxylamine hydrochloride. The mix-

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[10] Ray and Rieveschl, THIS JOURNAL, **65**, 836 (1943).

[11] Ray and Kreiser, *ibid.*, **67**, 504 (1945).

[12] Rieveschl, Ph.D. Thesis, University of Cincinnati, 1940.

ture was refluxed for two hours, then 200 cc. of water was added. The solution was boiled with Darco, filtered and the filtrate acidified with dilute hydrochloric acid while the solution was stirred vigorously. The yellow, somewhat gelatinous precipitate, after standing overnight, became crystalline. It was filtered, washed and dried in an oven at 70°. The yellow crystalline material melted at 284° (block). After recrystallizing from glacial acetic acid 41 g. or a 75% yield of pure material was obtained.

Anal. Calcd. for $C_{14}H_9O_3N$: N, 5.85. Found: N, 5.88.

Preparation of 9-Acetylaminofluorene-2-carboxylic Acid.—Ten g. (0.0417 mole) of the oxime of fluorenone-2-carboxylic acid was dissolved in 500 cc. of glacial acetic acid contained in a three-necked flask equipped with a reflux condenser and 20 g. (0.3 mole) of zinc dust was added in portions to the boiling solution over a period of one-half hour. The color changed from yellow to gray-green and then to colorless. After refluxing for one hour, 30 cc. (0.3 mole) of acetic anhydride was added dropwise, and the mixture refluxed for another hour. It was then filtered and the filtrate cooled and diluted with 200 cc. of water. The 9-acetylaminofluorene-2-carboxylic acid precipitated as white, fluffy material which was filtered, washed and dried. The crude product, weight 8.5 g., sintered at 340° (block). After recrystallization from glacial acetic acid, it sintered at 345°. The yield was 70%.

Anal. Calcd. for $C_{16}H_{13}O_3N$: N, 5.24. Found: N, 5.46.

Preparation of the Oxime of Methyl Fluorenone-2-carboxylate.—To a mixture of 400 cc. of benzene and 100 cc. of ethanol, 45 g. (0.189 mole) of the methyl ester of fluorenone-2-carboxylic acid,[12] 42 g. (0.213 mole) of barium carbonate, and 30 g. (0.43 mole) of hydroxylamine hydrochloride were added and the mixture boiled under reflux for three hours. The excess barium carbonate and barium chloride formed were filtered and washed with ethanol. Upon evaporation of the filtrate to one-fourth its volume, the oxime crystallized out. Recrystallization from xylene resulted in light yellow needles melting at 206–208° and weighing 28 g. or 59%.

Anal. Calcd. for $C_{15}H_{11}O_3N$: N, 5.53. Found: N, 5.41.

Preparation of Methyl 9-Aminofluorene-2-carboxylate.—Twenty-eight grams (0.11 mole) of the oxime prepared above was dissolved in 1 liter of ethanol. Over a period of three-quarters of an hour 100 cc. of concentrated hydrochloric acid and 50 cc. of water were added dropwise while 80 g. (1.2 mole) of zinc dust was introduced in small portions. After refluxing for a total of one and one-half hours, the solution was filtered to remove the zinc and cooled. The hydrochloride of the amine crystallized out as a white fluffy material weighing 30 g. and sintering at 230°. It was recrystallized from ethanol.

The free amine was prepared by stirring a suspension of 25 g. of the amine hydrochloride in 100 cc. of water, then adding 600 cc. of 3% sodium hydroxide solution and stirring for half an hour. The amine was filtered, washed and dried. After recrystallization from petroleum ether (b. p. 70–90°), 12 g. of free amine melting at 98–100° was obtained.

Anal. Calcd. for $C_{15}H_{13}O_2N$: C, 75.3; H, 5.48; N, 5.85. Found: C, 75.2; H, 5.61; N, 5.56.

Resolution of Methyl 9-Aminofluorene-2-carboxylate.—Five grams (0.0209 mole) of methyl 9-aminofluorene-2-carboxylate and 3.1366 g. (0.0209 mole) of *d*-tartaric acid were dissolved separately in 50 cc. of ethanol. The solutions were poured together and refluxed. More ethanol to make a total volume of 750 cc. was added in order to dissolve the salt formed. The solution was allowed to cool very slowly overnight. The next day the white crystals formed were filtered, washed with ethanol and dried. The weight of this material was 3.5 g. After recrystallizing twice from ethanol, it began decomposing at 195° and sintered at 210°.

Anal. Calcd. for $C_{30}H_{26}O_4N_2 \cdot C_4H_6O_6$: N, 4.70. Found: N, 4.60.

This salt was stirred with 30 cc. of 3% sodium hydroxide solution for several minutes. The free amine (m. p. 95°) was filtered, washed thoroughly and pressed dry. After drying for two hours it was weighed and dissolved in ethanol without warming the solvent. The rotations obtained are shown in Table II.

The original mother liquor was evaporated to a volume of 650 cc. and allowed to cool slowly. A second fraction of salt, weighing 2.5 g., m. p. 185–210° (with decomposition), was obtained.

Anal. Calcd. for $C_{45}H_{39}O_6N_3 \cdot C_8H_{12}O_{12}$: N, 4.33. Found: N, 4.02.

Upon treating similarly to the first fraction, the amine (m. p. 98°) was obtained. The original mother liquor was then evaporated to 100 cc. A third fraction of salt (m. p. 195–203°) weighing 2.0 g. was obtained.

Anal. Calcd. for $C_{15}H_{13}O_2N \cdot C_4H_6O_6$: N, 3.75. Found: N, 3.84.

This salt was treated in a similar fashion. The rotations of the amine (m. p. 92–95°) are shown in Table II.

Summary

Our resolution of the first optically active fluorene compound, 9-hydroxyfluorene-2-carboxylic acid,[11] has now been followed by the resolution of methyl 9-aminofluorene-2-carboxylate into its antipodes.

The difficulties in the resolution of this amino compound suggest that ready racemization prevented previous investigators from isolating optically active forms of fluorene compounds.

There is thus no reason why the classical methods of stereochemistry should not be employed in further study of the spatial configuration of fluorene.

CINCINNATI 21, OHIO

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