

thyl carbamates have been deacetylated by suspension in alkali. The resulting cellulose carbamates and  $\alpha$ -naphthyl carbamates containing free hydroxyl groups are soluble in organic solvents, indicating a difference in distribution of sub-

stituent groups as compared with insoluble derivatives of similar composition prepared by reaction of cellulose with insufficient quantities of reagent to produce complete esterification.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF CINCINNATI]

## Alkamine Esters of Fluorenonecarboxylic Acids<sup>1</sup>

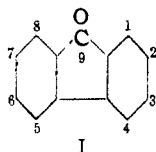
BY FRANCIS EARL RAY AND GEORGE RIEVESCHL, JR.<sup>2</sup>

Alkamine esters of diphenic acid<sup>3</sup> and of 9-substituted fluorene have been reported to possess local anesthetic action. For example, 9-aminofluorene<sup>4</sup> and 9-R-9-aminofluorenes<sup>5</sup> where R is methyl, phenyl or  $\alpha$ -naphthyl have a numbing effect when applied to the tongue. Alkamine esters of 9-fluorenonecarboxylic acid have also been the subject of several investigations and patents.<sup>6</sup>

Certain ketones, such as  $\beta$ -N-piperidinoethyl phenyl ketone<sup>7</sup> and 3-amino-4-methylphenyl isobutyl ketone,<sup>8</sup> are also active.

We have tested esters of fluorenonecarboxylic acids which incorporate the keto group in the molecule and have the carboxyl attached directly to the aromatic nucleus<sup>9</sup> and have found them to be active.

There are four isomeric fluorenonecarboxylic acids, corresponding to the positions 1, 2, 3, and 4, I. We have prepared derivatives of the 1, 2, and 4-carboxylic acids.



The following flow sheets show the methods of preparation of the esters and Table I lists the individual compounds and their properties.

(1) Abstracted from a thesis submitted to the faculty of the Graduate School of the University of Cincinnati by George Rieveschl, Jr., in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

(2) Laws Fellow 1938-40.

(3) Roberts and Johnson, *THIS JOURNAL*, **47**, 1396 (1925).

(4) Nakamura, *Sci. Papers Inst. Phys. Chem. Research (Tokyo)*, **14**, 184 (1930).

(5) Pinck and Hilbert, *THIS JOURNAL*, **59**, 8 (1937).

(6) Wolfes and Hromatka, U. S. Patent 2,221,828 (1941); Searle, U. S. Patent 2,262,754 (1941); Bockmuhl and Ehrhart, U. S. Patent 2,230,774 (1941); cf. the following, German Patents 656,784, 657,529 (1938); French Patent 840,824; Swiss Patent, 202,665 (1939).

(7) Mannich and Lammering, *Ber.*, **55**, 3515 (1922); Mannich and Curtas, *Arch. Pharm.*, **264**, 750 (1926); Blicke and Blake, *THIS JOURNAL*, **52**, 235 (1930).

(8) Hartung and Munch, *ibid.*, **51**, 2570 (1929).

(9) Kamm, *ibid.*, **42**, 1030 (1920).

TABLE I

Esters of	M. p. of hydrochloride, °C.	Cl analyses, %		Color
		Calcd.	Found	
Fluorenone-1-carboxylate				
$\beta$ -Diethylaminoethyl	194-195	9.85	10.18	Yellow
$\gamma$ -Diethylaminopropyl	159-160	9.48	9.49	Yellow
Fluorenone-4-carboxylate				
$\beta$ -Diethylaminoethyl	194-196	9.85	9.97	Yellow
$\gamma$ -Diethylaminopropyl	210-211	9.48	9.32	Yellow
Fluorenone-2-carboxylate				
$\beta$ -Diethylaminoethyl	223-224 <sup>a</sup>	9.85	9.80	Yellow
$\gamma$ -Diethylaminopropyl	221-222	9.68	9.46	Yellow
$\beta$ -Dibutylaminoethyl	179-180	8.52	8.33	Yellow
$\beta$ -Dimethylaminoethyl	222-224 <sup>a</sup>			
Oximes of esters of		N	N	
Fluorenone-2-carboxylate				
$\beta$ -Diethylaminoethyl	231-232	7.47	7.28	
$\gamma$ -Diethylaminoethyl	219-220 (di-HCl)	6.59	6.85	
Ester of				
Fluorene-2-carboxylate				
$\beta$ -Diethylaminoethyl	204-206	8.26	8.12	

<sup>a</sup> Mixed m. p. 186-192°.

The oximes of these amino alcohol esters of fluorenonecarboxylic acids may be prepared readily without hydrolysis of the ester group by operating in a nearly neutral solution. The oximes are more active anesthetics than the parent compounds. This is the first time, so far as we have been able to find, that the oximino group has been reported to increase the anesthetic potency of a ketone. In addition the increased solubility of the compounds thus produced and the more nearly neutral character of their hydrochlorides in solution add to their effectiveness.

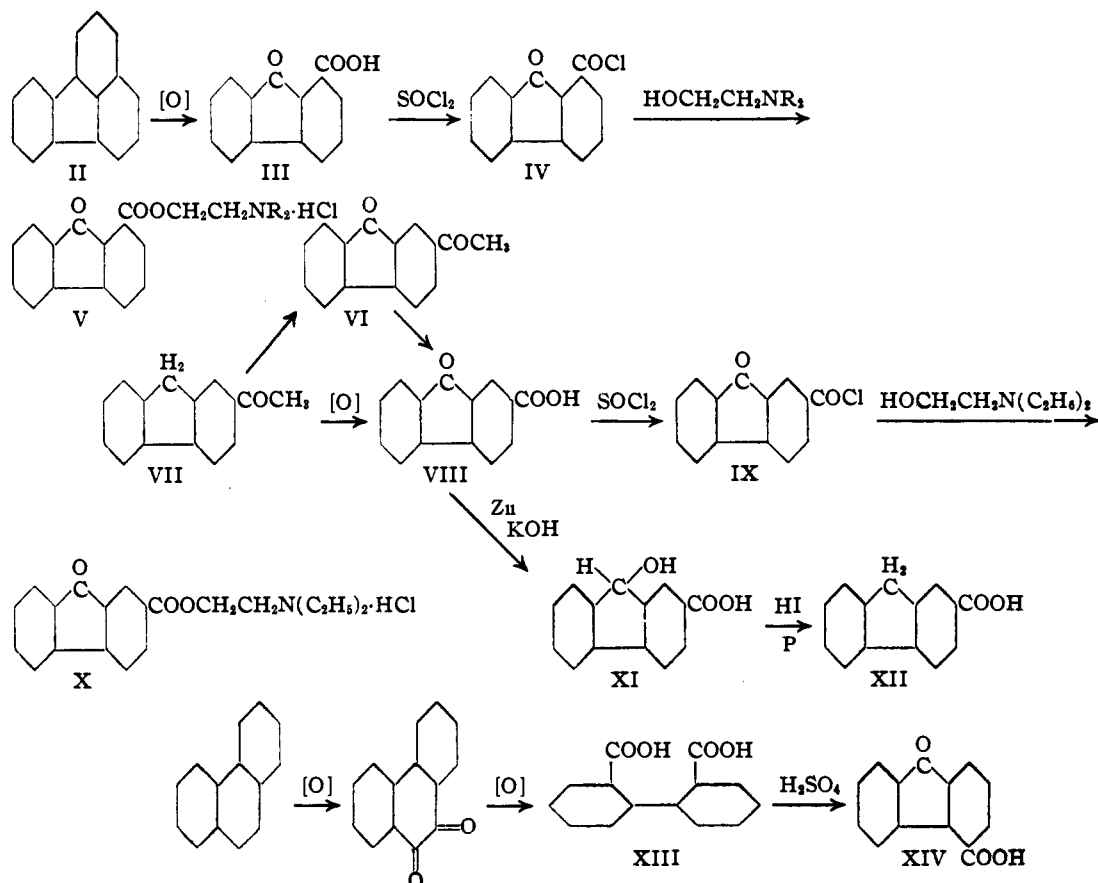
Fluorenone-2-carboxylic acid was reduced to fluorene-2-carboxylic acid and the  $\beta$ -diethylaminoethyl ester prepared. It proved to be somewhat more soluble than the corresponding fluorenone.

### Experimental

Fluorenone-2-carboxylic acid, VIII, was prepared by Fortner<sup>10</sup> by the oxidation of fluorene-2-carboxylic acid Hinkel, Ayling and Beynon,<sup>11</sup> employing a modified

(10) Fortner, *Monatsh.*, **25**, 443 (1904).

(11) Hinkel, Ayling and Beynon, *J. Chem. Soc.*, 339 (1936).



Gattermann synthesis by the reaction of liquid hydrogen cyanide, aluminum chloride, hydrogen chloride and fluorene in chlorobenzene, obtained a yield of 70% of 2-fluorenealdehyde. Dziejowski and Schnayder<sup>12</sup> had prepared 2-acetylfluorene by a Friedel-Crafts reaction between fluorene, acetyl chloride and aluminum chloride in carbon disulfide solution. A yield of only 8% was reported. Oxidation gave fluorenone-2-carboxylic acid but the yield was not stated.

Despite the low yield of 2-acetylfluorene, previous experience in this Laboratory<sup>13</sup> had convinced us that this type of reaction could be made to give good yields. After many trials we found that acetic anhydride gave much better results than acetyl chloride and by carrying the reaction out in boiling carbon disulfide a quantitative yield of crude 2-acetylfluorene resulted.

Ardashev, Lomovatskaya and Kacher<sup>14</sup> have reported yields of 50% using acetyl chloride, fluorene and aluminum chloride in nitrobenzene solution. More recently Bachmann and Sheehan,<sup>15</sup> also using nitrobenzene as a solvent, treated fluorene with acetic anhydride in the presence of aluminum chloride to produce acetylfluorene.

We had tried nitrobenzene as a solvent but the trouble-

some steam distillation required led us, after many trials, to adopt the following procedure.

**2-Acetylfluorene, VII.**—Crude fluorene (m. p. 100–107°) was used: 80 g. (0.48 mole) was dissolved in 350 cc. of carbon disulfide and a 0.25 lb. (113 g.) bottle of aluminum chloride was added. A dark red color developed. Redistilled acetic anhydride (37.8 cc., 0.41 mole) was added slowly. If the reaction did not start spontaneously, the flask was warmed in a hot water-bath. The acetic anhydride was added at a sufficient rate to maintain the liquid in gentle reflux. The whole must be well stirred during the addition of the acetic anhydride which takes forty-five to sixty minutes and during the subsequent heating for one hour on the water-bath.

The heavy, dark green mass was filtered and pressed dry. It was then stirred with sufficient carbon disulfide to just cover it. It was again filtered and washed with two 50-cc. portions of carbon disulfide. This step is of the utmost importance, as it effectively removes tars and other impurities and obviates the use of pure fluorene.

After the removal of the carbon disulfide the material was added in portions to a stirred solution of 30 cc. of concentrated hydrochloric acid in 800 cc. of water. The crude 2-acetylfluorene was washed and air dried. It weighed 100–110 g. and could be oxidized directly to fluorenone-2-carboxylic acid.

Recrystallization from alcohol gave a white compound that melted at 132°. This is the same as previously reported.<sup>13</sup>

(12) Dziejowski and Schnayder, *Bull. intern. acad. polon. sci. Classe sci. math. nat.*, 529 (1934).

(13) Ray and Rieveschl, *THIS JOURNAL*, 60, 2675 (1938).

(14) Ardashev, Lomovatskaya and Kacher, *J. Applied Chem. (U. S. S. R.)*, 11, 1344 (1938).

(15) Bachmann and Sheehan, *THIS JOURNAL*, 62, 2688 (1940).

**Fluorenone-2-carboxylic Acid, VIII.**—The entire yield from the previous preparation was dissolved in 650 cc. of acetic acid and oxidized with 450 g. of sodium dichromate. When the reaction moderated, showing the completion of oxidation at the 9-carbon, 200 cc. of acetic anhydride was slowly added while the whole was maintained at gentle reflux. Heating was continued for six hours more.

The reaction mixture was poured into 2.5 gallons of hot water, digested for thirty to sixty minutes, filtered and washed with very dilute sulfuric acid to remove chromium salts. It was transferred wet to 700 cc. of 5% potassium hydroxide, heated to 80° with Darco and filtered hot.

The alkaline solution was acidified at 80–90°, and the fluorenone-2-carboxylic acid precipitated as a thick lemon-yellow mass. The yield was 30–35 g., but the alkali insoluble material was mostly 2-acetylfluorenone and could be oxidized to yield 23 to 27 g. of fluorenone-2-carboxylic acid. The total yield was, therefore, 58–62% based on the original fluorene. It was best recrystallized from acetic anhydride from which it was obtained in fine canary colored crystals melting with partial sublimation (block) at 339–341°. It may also be recrystallized from "Cello-solve."

**2-Acetylfluorenone, VI.**—This previously unreported compound was the major portion of the alkali insoluble material. It was recrystallized from alcohol and melted at 154–155°.

*Anal.* Calcd. for  $C_{16}H_{10}O_2$ : C, 81.02; H, 4.53. Found: C, 81.30; H, 4.72.

**Fluorenone-2-carbonyl Chloride, IX.**—This was prepared by treating the acid, VIII, with pure thionyl chloride. The crude material melted at 174–176°. When recrystallized from benzene or toluene it melted at 183–184° and formed golden-yellow plates.

*Anal.* Calcd. for  $C_{14}H_7O_2Cl$ : Cl, 14.62. Found: Cl, 14.51.

The methyl ester was prepared by treating the acid chloride with excess methyl alcohol. The long yellow crystals from methyl alcohol melted at 185–186°. Fortner<sup>10</sup> reported 181°.

**$\beta$ -Diethylaminoethylfluorenone-2-carboxylate Hydrochloride, X.**—As the properties of aminoalcohol esters of fluorenone-2-carboxylic acid are listed in Table I, a typical preparation only will be described.

A solution of 12.2 g. of fluorenone-2-carbonyl chloride in 200 cc. of dry benzene was prepared. To this was added 6.0 g. of  $\beta$ -diethylaminoethyl alcohol in 45 cc. of benzene. The reaction was vigorous and the hydrochloride of the ester separated as a yellow solid. The filtered precipitate was washed with ether and recrystallized from methyl alcohol to which hydrogen chloride had been added. It melted at 223–224°. The yield of crude material melting at 212–214° was quantitative (18 g.).

**The Oxime of  $\beta$ -Diethylaminoethylfluorenone-2-carboxylate Hydrochloride.**—The crude ester may be used if desired. A mixture of 14.4 g. of  $\beta$ -diethylaminoethyl fluorenone-2-carboxylate hydrochloride, 4.2 g. of hydroxylamine hydrochloride, 14 g. of powdered barium carbonate and 125 cc. of methyl alcohol was refluxed for three hours. The yellow color of the solution soon faded completely. The barium carbonate was removed by filtration and

washed with methyl alcohol. The solution, after treatment with Darco, deposited 8 g. of fluffy white oxime decomposing at 224–226°. Recrystallization from methyl alcohol gave 6 g. melting at 231–232°.

**Fluorenone-1-carboxylic acid, III,** was prepared by the method of Fieser and Seligman.<sup>16</sup> It melted at 193–194°. The yield of bright orange crystals was 52%.

**Fluorenone-1-carbonyl chloride, IV,** was prepared as described for the 2-isomer. It was a bright yellow solid melting at 130–132°. Goldschmidt<sup>17</sup> reported a melting point of 140°.

**Fluorenone-4-carboxylic Acid, XIV.**—This substance was prepared from diphenic acid by the method of Moore and Huntress.<sup>18</sup> The yield was 96% of a material melting at 224–225°. Moore and Huntress give 223–224°. When recrystallized twice from ethyl alcohol it melted at 227°. The esters were prepared in the same manner as described for fluorenone-2-carboxylic acid.

**Fluorene-2-carboxylic Acid, XII.**—Fortner<sup>10</sup> had prepared this acid from 2-aminofluorene by the Gattermann reaction. We prepared it by the reduction of fluorenone-2-carboxylic acid. After a number of trials it was found best to reduce it in two steps. Fluorenone-2-carboxylic acid resulted when a mixture of 22 g. of fluorenone-2-carboxylic acid and 22 g. of potassium hydroxide in 400 cc. of alcohol and 200 cc. of water was boiled with 50 g. of zinc dust for nine hours. The filtrate was heated with Darco and acidified with 250 cc. of concentrated hydrochloric acid. A white powder that sinters at 224–240° was obtained in a yield of 21 g. Fluorenone-2-carboxylic acid, XI, is much more soluble in alcohol than the keto-acid. It was reduced in 300 cc. of glacial acetic acid with 38 g. of iodine and 6 g. of red phosphorus by boiling for twelve hours. After filtration 11.0 g. of fluorene-2-carboxylic acid was deposited and an additional 2.5 g. was obtained from the mother liquor. It melted at 262–267° with decomposition. Fortner<sup>14</sup> gives 260° dec. for fluorene-2-carboxylic acid. It was converted to the acid chloride by heating for thirty minutes with 20 cc. of thionyl chloride, the excess thionyl chloride was distilled and the gray residue was recrystallized from benzene. It melted at 182°. A small amount was treated with methyl alcohol and the methyl ester after recrystallization from methyl alcohol melted at 122°. Fortner<sup>10</sup> gives 120° for methyl fluorene-2-carboxylate. The main portion of the acid chloride was treated with  $\beta$ -diethylaminoethyl alcohol as described for the previous compounds (Table I).

### Summary

A practical synthesis of fluorenone-2-carboxylic acid has been developed.

A number of alkylaminoalkyl esters of 1, 2 and 4-fluorenonecarboxylic acids have been prepared as well as the  $\beta$ -diethylaminoethyl ester of fluorene-2-carboxylic acid (Table I).

The important observation that the oxime group may increase the local anesthetic activity of a ketone has been noted for the first time.

(16) Fieser and Seligman, *THIS JOURNAL*, **57**, 2174 (1935).

(17) Goldschmidt, *Monatsh.*, **23**, 885 (1902).

(18) Moore and Huntress, *THIS JOURNAL*, **49**, 1329 (1927).

Many of these compounds have considerable local anesthetic and antispasmodic properties, the details of which will be reported later.

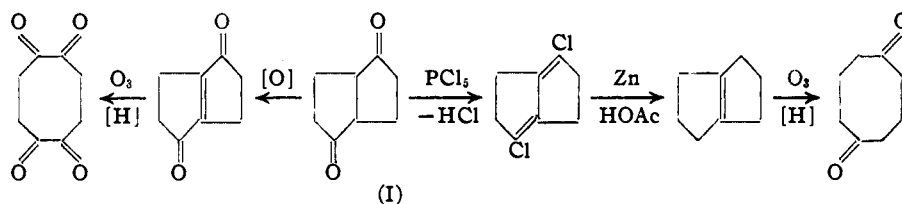
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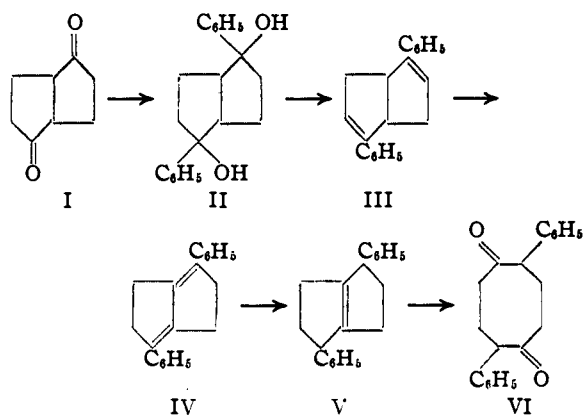
[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

A Synthesis of 2,6-Diphenylcyclooctandione-1,5<sup>1a</sup>BY STANLEY WAWZONEK<sup>1b</sup>

The successful synthesis of *sym*-dibenzocyclooctandione-5,11 from dibenzosuccindandione-9,12<sup>2</sup> suggested the possibility that less substituted 1,5-diketocyclooctanes might be prepared from bicyclo-[3,0,3]-octandione-2,6 (I) by similar reactions, and subsequently used in the syntheses of cyclooctatetraenes.



Attempts to synthesize cyclooctandione-1,5 and cyclooctantetraone-1,2,5,6 by such methods, shown below, failed because of the instability of compounds obtained in the first step in each case. The synthesis of 2,6-diphenylcyclooctandione-1,5 (VI), however, proved successful and is summarized in Formulas I-VI.

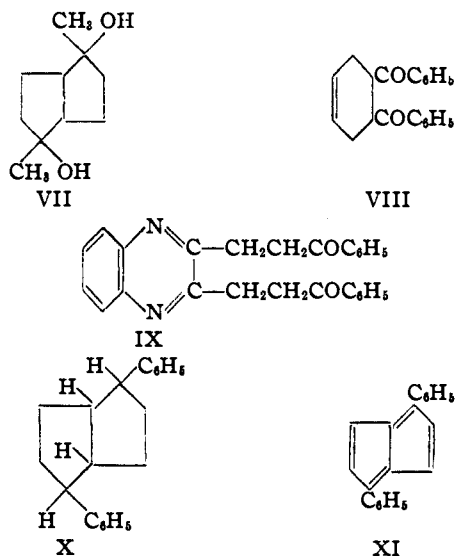


Treatment of bicyclo-[3,0,3]-octandione-2,6 (I) with phenylmagnesium bromide gave 2,6-diphenyl-2,6-dihydroxybicyclo-[3,0,3]-octane (II). The dicarbinol (II) formed chromophoric salts with mineral acids and gave a dimethyl ether

when treated in methanol with a trace of sulfuric acid. Dehydration of the dicarbinol (II) with either potassium bisulfate or formic acid, gave 2,6-diphenylbicyclo-[3,0,3]-octadiene-2,6 (III). A similar dehydration when tried with 2,6-dimethyl-2,6-dihydroxybicyclo-[3,0,3]-octane (VII), obtained by adding methylmagnesium iodide to

the diketone (I), gave unstable terpene-like oils. Proof for the structure of the diene (III) was its oxidation by chromic acid to 2,3-dibenzoyladipic

acid. This same acid was obtained from the chromic acid oxidation of 4,5-dibenzoylcyclohexene (VIII).<sup>3</sup> The course of the dehydration



of the dicarbinol (II) indicates that the 2,6-hydroxyl groups and the 1,5-hydrogen atoms, present in this compound, must have a *cis*-configuration.

Rearrangement of the diene (III) into the higher-melting conjugated diene, 2,6-diphenylbicyclo-[3,0,3]-octadiene-1,5 (IV) was accom-

(1a) Presented before the Division of Organic Chemistry of the American Chemical Society at the Detroit meeting, April, 1943.

(1b) National Research Council Fellow, 1940-1941.

(2) Wawzonek, *This Journal*, **62**, 745 (1940).

(3) Adams and Gold, *ibid.*, **62**, 56 (1940).