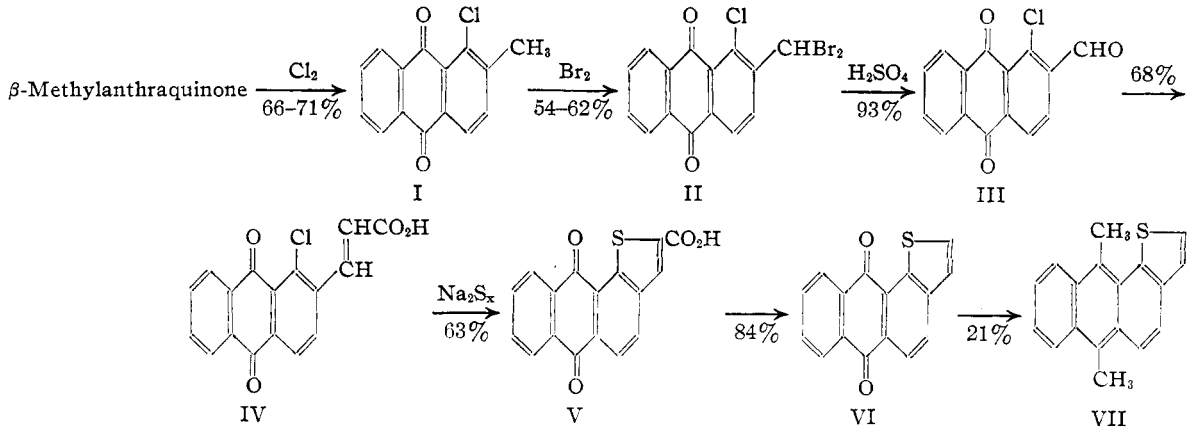
[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF HARVARD UNIVERSITY]

Isologs of 9,10-Dimethyl-1,2-benzanthracene Containing Sulfur and Selenium

BY E. B. HERSHBERG[1] AND LOUIS F. FIESER

A paper by Sandin and one of us[2] reported the synthesis of 4,9-dimethyl-5,6-benzthiophanthrene, a compound differing from the carcinogenic 9,10-dimethyl-1,2-benzanthracene in the replacement of the terminal ring of the anthracenoid system by a thiophene ring. Tests conducted by Drs. Shields Warren and C. E. Dunlap[3] have shown this thiophene isolog to be highly carcinogenic. In an initial experiment in which the substance was administered by injection in tricaprylin solution, tumors were produced in all of six mice (effective total) in an average time of eighteen weeks, as compared with the latent period of fourteen weeks observed with the corresponding hydrocarbon. Such a marked propensity to produce tumors at the site of administration has been encountered previously only among fully carbocyclic compounds. The investigation of other heterocyclic substances is thus a matter of interest, and in taking up further work in this direction we have sought syntheses adaptable to the introduction of radioactive sulfur as a tracer element.



A route to isologs of 9,10-dimethyl-1,2-benzanthracene in which the 1,2-benz ring is replaced by a heterocycle was patterned in part after methods described in the patent literature. β-Methylanthraquinone was chlorinated in 3% oleum at a low temperature by an adaptation of a patented procedure,[4] but the product was found to require more extensive purification than had been indicated before being suitable for bromination. This reaction was conducted in nitrobenzene at 170–175°, following in part the directions of Ullmann and Bincer.[5] A trial hydrolysis of the dibromide (II) with ferric chloride in acetic acid according to a patent[6] gave the aldehyde (III) in only 59% yield and the material insoluble in bisulfite solution gave no appreciable amount of III on further treatment. Very satisfactory results were obtained by hydrolysis with hot sulfuric acid, following the method described by Ullmann and Bincer[5] for small-scale runs. The preparation of the acrylic acid (IV) by condensation of the aldehyde with sodium acetate and acetic anhydride according to a patent[7] gave mediocre results in preliminary tests, but the product was obtained satisfactorily by condensation of III with malonic acid in the presence of pyridine.

Cyclization to the carboxythiopheno derivative (V) with sodium polysulfide was accomplished substantially by the method of Lulek and Belcher.[8] Decarboxylation by the copper-quinoline method gave the hitherto unreported 1,2-(thiopheno-2′,3′)-anthraquinone (VI). The introduction of two mesomethyl groups was then accomplished by

(1) Research Fellow on grants from the National Advisory Cancer Council and the Eli Lilly Company.

(2) Sandin and Fieser, THIS JOURNAL, **62**, 3098 (1940).

(3) On a grant from the Jane Coffin Childs Memorial Fund for Medical Research.

(4) Thomas, U. S. Patent 1,504,164 (1924); Smith, Primrose and Thomas, British Patent 335,232 (1930).

(5) Ullmann and Bincer, *Ber.*, **49**, 732 (1916).

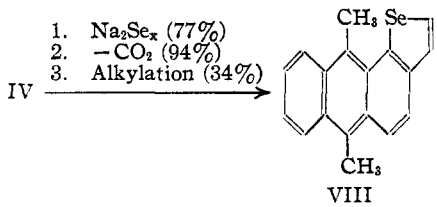
(6) Wilke, German Patent 361,043 (1920).

(7) Friedr. Bayer and Co., German Patent 282,265 (1913).

(8) Lulek and Belcher, U. S. Patent 2,097,860 (1937).

the sequence of reactions developed by Sandin.[2] After interaction of the quinone VI with excess methyl Grignard reagent, treatment of the resulting magnesio halide derivative of the diol with hydriodic and acetic acids gave a solid methyliodomethyl compound and this on reduction with stannous chloride in dioxane afforded the desired end-product VII. 9,10-Dimethyl-1,2-(thiopheno-2′,3′)-anthracene resembles the corresponding hydrocarbon and forms a purple-black semipicrate and a red trinitrobenzene derivative.

The selenium isolog (VIII) was similarly prepared through two intermediates, the first of which is reported in the patent by Lulek and Belcher.[8]



VIII

Experimental Part[9]

1-Chloro-2-methylanthraquinone (I).—A 100-g. lot of purified β-methylanthraquinone[10] was dissolved with 2 g. of iodine in 400 cc. of 3% oleum contained in a three-necked flask provided with a platinum wire stirrer working through a seal containing sulfuric acid. Chlorine was led in at one side tubulature, and the other was connected to an escape trap consisting of a U-tube partly filled with carbon tetrachloride. The deep red-brown slurry was stirred mechanically and kept at 3–5° (inside temperature) while chlorine was passed in at a slight positive pressure for a total of six hours. The absorption of chlorine, as noted from the increase in flow at the escape trap when the stirrer was stopped, fell off markedly after three hours.

Finally the sulfuric acid solution was poured onto 2 liters of cracked ice and the light yellow precipitate was collected, washed free of acid and dissolved while still moist in 1 liter of acetic acid under reflux. The solution was diluted with 120 cc. of water and allowed to cool, when 99 g. (86%) of the crude chloro compound separated in long fine needles, m. p. 157–159°. This material is not satisfactory for the bromination and gives only negligible yields of the dibromomethyl compound. One or two more crystallizations from dilute acetic acid as above usually were necessary to remove an interfering impurity (iodine?). The purification was attended with a loss of 15–20% of the product and resulted in but little improvement in the melting point. The material thus obtained was suitable for bromination but was still contaminated with other products, for six recrystallizations of a small sample from benzene–ligroin were required to give the pure quinone in the form of clusters of short yellow needles, m. p. 172.3–172.8° (Ullmann and Bincer,[5] 171.5°, corr.).

1-Chloro-ω-dibromo-2-methylanthraquinone (II).—A solution of 40 g. of partially purified I in 200 cc. of nitrobenzene was heated to 170–175° and 30 cc. of bromine was added dropwise over two hours. Heating was continued for ten hours longer and then a stream of nitrogen was passed over the hot solution to remove excess bromine. The bromine-free solution was cooled to about 110–120° and poured into 1200 cc. of alcohol which had been heated nearly to the boiling point. There separated 40–50 g. of the dibromide in the form of shining, light brown plates, m. p. 165–170°. Recrystallization was best effected by dissolving the product in 130–150 cc. of boiling benzene and pouring the solution into 1 liter of hot alcohol. This gave 35–40 g. (54–64%) of yellow plates, m. p. 175–178°. A sample recrystallized three times more from acetic acid formed glistening yellow plates, m. p. 179.3–179.8°, in agreement with Ullmann and Bincer.[5]

1-Chloroanthraquinone-2-aldehyde (III).—In a typical run 19.2 g. of the dibromide II was dissolved in 150 cc. of concentrated sulfuric acid and the solution was heated for ten minutes at 120° under a slow stream of nitrogen and with occasional shaking to facilitate the removal of bromine. The temperature was then gradually raised to 130° in the course of fifteen minutes, after which no more bromine was seen in the emergent gas. The cooled solution was poured onto 2 l. of cracked ice and the yellow precipitate was collected, washed substantially free of acid, and treated while still moist with 2–2.5 l. of boiling water containing 30–35 g. of sodium bisulfite. Almost all of the solid dissolved and a clear yellow solution resulted on filtration. This was acidified with hydrochloric acid and warmed on the steam-bath for one hour to coagulate the precipitated solid. The material when dried in vacuum weighed 11.6 g. (93%) and melted at 196–198°. Five crystallizations of a small sample gave slender yellow needles, m. p. 199.6–200.1° (U. and B.,[5] 198.5°).

1-Chloroanthraquinone-2-acrylic Acid (IV).—A 125-cc. round-bottomed flask was suspended in a Woods metal bath at 100° and charged with 6.4 g. of 1-chloroanthraquinone-2-aldehyde, 18 cc. of pyridine, and 10 g. of malonic acid. The solid soon dissolved and then, after two to three minutes and with increased gas evolution and foaming, the mixture suddenly set to a pasty mass. This was heated for one hour with occasional stirring with a spatula, 3 cc. of pyridine and 5 g. of malonic acid were added, and the mixture was heated and stirred for one hour longer and then added to 400–500 cc. of water containing excess hydrochloric acid. The product was collected and washed thoroughly with alcohol, which removes a soluble impurity. Crystallization of the crude material from 500 cc. of acetic acid gave 5.0 g. (68%) of pure IV, m. p. 286.5–287.5°, dec. It forms very fine yellow needles.

Anal. Calcd. for $C_{17}H_9O_4Cl$: C, 65.30; H, 2.90; Cl, 11.34. Found: C, 65.14; H, 3.29; Cl, 11.54.

1,2-(Thiopheno-2′,3′)-anthraquinone-5′-carboxylic Acid (V).—A mixture of 1.5 g. of IV, 0.45 g. of powdered sulfur, 3.6 g. of hydrated sodium sulfide, 15 cc. of water, and 0.9 cc. of 6 *N* sodium hydroxide was refluxed for fifteen hours in a bath at 130°. A clear, deep greenish-brown solution

(9) Microanalyses by Eleanor Werble. All melting points are corrected.

(10) Practical grade material (Eastman Kodak Co.) was distilled at the water pump and the light yellow distillate, b. p. 236–238° at 10 mm., poured into Pyrex dishes and so obtained in a thin layer which could be removed easily and ground to a fine powder, m. p. 173–176°.

resulted at the outset and a solid salt of the reaction product soon began to separate. Termination of the reaction before the time specified, however, resulted in a lower yield. The mixture was eventually cooled and the solid collected with suction on a hardened filter paper and washed with saturated sodium chloride solution. The salt was digested with 500 cc. of water at the boiling point and the solution filtered from an insoluble residue (from later experiments with the selenium analog it was recognized that this residue contains some of the free acid). Acidification gave a gelatinous precipitate which was coagulated as much as possible by boiling the suspension. The mixture was filtered by suction while still hot, with care not to allow the solid to pack too tightly. The washed product while still moist was placed in the alundum thimble of a continuous extractor and dissolved in about 300 cc. of acetic acid. The solution was concentrated to the point of crystallization and allowed to cool, when 0.93 g. (63%) of very fine, yellow needles was obtained. When heated in a capillary in an aluminum block the substance darkened and agglomerated at 345°–50° and melted at 361–363°, dec.

Anal. Calcd. for $C_{17}H_8O_4S$: C, 66.23; H, 2.62; S, 10.40. Found: C, 66.07; H, 2.97; S, 10.71.

1,2-(Thiopheno-2′,3′)-anthraquinone (VI).—Decarboxylation was accomplished smoothly by heating 0.86 g. of V in 5 cc. of quinoline at 230–240° and adding 50 mg. of basic copper carbonate in small portions. After twenty to thirty minutes, when the evolution of carbon dioxide had ceased, the solution was cooled and poured into dilute hydrochloric acid. The precipitated brownish-yellow solid when crystallized from dilute acetic acid (Darco) afforded 0.62 g. (84%) of the quinone VI, m. p. 218.5–219.5°. A small sample when recrystallized twice from alcohol formed slender yellow needles melting constantly at 219.6–220.1°. The quinone gives an orange vat with alkaline hydrosulfite.

Anal. Calcd. for $C_{16}H_8O_2S$: C, 72.71; H, 3.05; S, 12.13; mol. weight, 264. Found: C, 72.84; H, 3.15; S, 11.84; mol. weight (micro-Rast), 260.

9,10-Dimethyl-1,2-(thiopheno-2′,3′)-anthracene (VII).—To a solution of 1.3 g. of the anthraquinone VI in 15 cc. of benzene was added 25 cc. of an 0.8 *N* solution of methylmagnesium chloride in ether. The flask was stoppered and warmed in a water-bath at 70–80° for one hour. The orange solution was cooled and treated with a mixture of 15 cc. of constant boiling hydriodic acid and 25 cc. of acetic acid, and the benzene and ether were removed by evacuation at the water pump, the temperature of the liquid being kept at 10–15°. The iodomethyl compound separated as a yellow solid, which was collected, washed with dilute acetic acid, and dissolved in 100 cc. of dioxane. The solution is very sensitive to light and darkens rapidly; it was therefore treated at once with a solution of 10 g. of hydrated stannous chloride and 30 cc. of concentrated hydrochloric acid in 50 cc. of dioxane. On brief refluxing the color faded to a pale yellow. The bulk of the dioxane was removed by distillation, water was added, and the solution cooled in an ice-bath, when a tarry solid separated. This was extracted several times with alcohol, and the clarified solution (Darco) on concentration afforded 0.48 g. (37%) of yellow solid, m. p. 116–120°. After two more crystallizations from petroleum ether (30–60°) there was obtained 0.27 g. (21%) of light yellow plates, m. p. 123.5–124.2°. The substance shows a bluish-white fluorescence in ultraviolet light. A sample crystallized further from alcohol and from petroleum ether formed pale yellow, diamond-shaped prisms, m. p. 123.6–124.2°.

Anal. Calcd. for $C_{18}H_{14}S$: C, 82.40; H, 5.38; S, 12.22. Found: C, 82.74; H, 5.72; S, 12.02.

When 25 mg. of the substance was treated in absolute alcohol with 50 mg. of picric acid, a **semipicrate** crystallized in the form of glistening, slender needles which appeared purple-black by transmitted light and jet black by reflected light. The substance melted at 125.5–126°.

Anal. Calcd. for $2C_{18}H_{14}S \cdot C_6H_3O_7N_3$: N, 5.57. Found: N, 5.76, 5.89.

The **trinitrobenzene derivative** crystallized from absolute alcohol in glistening, maroon-colored needles, m. p. 172.5–173°.

Anal. Calcd. for $C_{18}H_{14}S \cdot C_6N_3O_6N_3$: N, 8.84. Found: N, 8.76.

1,2-(Selenopheno-2′,3′)-anthraquinone-5-carboxylic Acid (VIII).—A slurry of 1.8 g. of powdered selenium in 20 cc. of warm absolute alcohol was treated with 1.6 g. of sodium with mechanical stirring. After the sodium had dissolved, 1.8 g. more selenium was added and the mixture was refluxed for one-half hour. The polyselenide solution was diluted with 10 cc. of water and treated with 2.5 g. of 1-chloroanthraquinone-2-acrylic acid, and the mixture was heated with stirring for four hours in a metal bath at 100–110°. A clear solution resulted at the outset, and a solid product soon began to separate. After cooling, the solid was collected, washed with 10% salt solution, and extracted with 1 l. of boiling water. The residual solid nearly all dissolved when extracted further with 500 cc. of hot water containing 2 g. of sodium carbonate. Acidification of the filtrates gave a curdy orange product which was coagulated by boiling, collected and dissolved while still wet in 1.5 l. of acetic acid. When concentrated to a volume of 300 cc. and cooled, the solution deposited 2.2 g. (77%) of orange needles, m. p. 347–349°, dec. Recrystallization from acetic acid gave fine yellow needles of the same melting point. The quinone gives a deep wine-colored vat.

Anal. Calcd. for $C_{17}H_8O_4Se$: C, 57.48; H, 2.27. Found: C, 57.24; H, 2.35.

1,2-(Selenopheno-2′,3′-anthraquinone (IX).—The decarboxylation of 0.5 g. of the acid was conducted by the method described above and was complete in four minutes at 230°. The precipitated and washed product when crystallized from dilute acetic acid gave 0.41 g. (94%) of brown needles, m. p. 212–214°. After two recrystallizations from benzene–ligroin the substance formed bronze-colored needles, m. p. 213.5–214.5°.

Anal. Calcd. for $C_{16}H_8O_2Se$: C, 61.75; H, 2.59. Found: C, 61.66; H, 2.86.

9,10-Dimethyl-1,2-(selenopheno-2′,3′)-anthracene (X).—A solution of 1.24 g. of the above quinone in 50 cc. of benzene was treated exactly as described for the sulfur isolog with methylmagnesium chloride, followed by hydriodic and acetic acids. The iodomethyl compound was less soluble than in the other series and about 200 cc. of dioxane was required to dissolve it. After reduction with stannous chloride and dilution with water, a fine, light yellow solid

separated and was collected after cooling at 0° for about two hours. A solution of the product in benzene was passed through a column of activated alumina and Super-Cel. No fluorescence was observed under ultraviolet light, but a dark brown layer of impurities was left at the top of the column and the principal zone was yellow and could be eluted readily with benzene. After complete removal of the benzene by evaporation, the residue was crystallized from a small volume of ether and gave 0.42 g. (34%) of small, yellow, microcrystalline clusters, m. p. 114–117°. The compound crystallizes much better from absolute alcohol, and after two more recrystallizations from this solvent it formed pale yellow plates, m. p. 118–118.5°. The pure substance shows a yellow fluorescence in ultraviolet light.

Anal. Calcd. for $C_{18}H_{14}Se$: C, 69.90; H, 4.56. Found: C, 69.98; H, 4.86.

The **picrate** forms dark brown needles from absolute alcohol, m. p. 145.5–146°.

Anal. Calcd. for $C_{18}H_{14}Se \cdot C_6H_3O_7N_3$: N, 7.81. Found: N, 7.75.

The **trinitrobenzene derivative** forms maroon-colored needles from absolute alcohol and melts at 173.5–174°.

Anal. Calcd. for $C_{18}H_{14}Se \cdot C_6H_3O_6N_3$: N, 8.05. Found: N, 8.17.

Summary

Syntheses are reported for isologs of 9,10-dimethyl-1,2-benzanthracene in which the 1,2-benz ring is replaced by a thiophene and by a selenophene ring.

CONVERSE MEMORIAL LABORATORY
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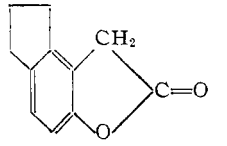
[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF TRINITY COLLEGE]

Fluorenone-2,3-dicarboxylic Acid and its Anhydride

BY WARREN C. LOTHROP AND JOHN A. COFFMAN

It has recently been suggested[1] that fluorenone-2,3-dicarboxylic anhydride would be of interest as an analog of phthalic acid. Moreover, the compound seemed of value to us as a test case involving the Mills–Nixon effect, inasmuch as it contains two five-membered rings on opposite sides of a benzene ring. Such an arrangement would impose some strain on one of these rings which would very likely manifest itself in some instability of the anhydride ring, although it is not to be anticipated from previous work[2] that this strain would be very great.

Examples of similar compounds are few and ambiguous. While pyromellitic acid readily forms a di-anhydride and a di-imide, indicating no strain, a case more comparable with our own has recently been reported[3] where a Mills–Nixon strain is apparently operative: the formation of lactones I and II from the corresponding hydroxy acids proceeding in the former case spontaneously but in the latter only upon heating with concentrated sulfuric acid.



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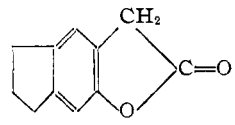
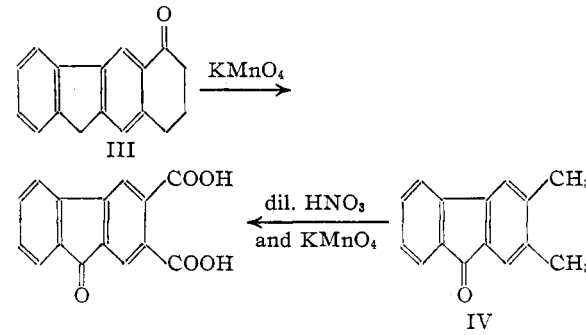


II

The preparation of the desired dicarboxylic acid was found to involve considerable difficulty although it was finally achieved by two independent methods, using oxidations of ketotetrahydrobenzofluorene (III) and of 2,3-dimethylfluorenone (IV)



The first method proved unsatisfactory only because of the last step, since the previously prepared[4] compound III was readily obtained in good yield by ring closure of γ-2-fluorylbutyric acid with anhydrous hydrogen fluoride. Oxidation of III by various reagents (dilute nitric acid, potassium dichromate in acetic acid, potassium permanganate in acid solution or in acetone, and selenium dioxide in dioxane) gave resins or unreacted material. Only alkaline permanganate

(1) Rieveschl and Ray, *Chem. Rev.*, **23**, 365 (1938); but see Dziewonski, Kuzdrzal and Mayer, *Bull. Acad. Polonaise*, **348A** (1934), regarding failure to obtain 2,3-diacetylfluorene, the most likely starting material.

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

(3) Arventi, *Ann. sci. univ. Jassy*, Pt. I, **25**, 692 (1939).

(4) Koelsch, THIS JOURNAL, **55**, 3885 (1933).