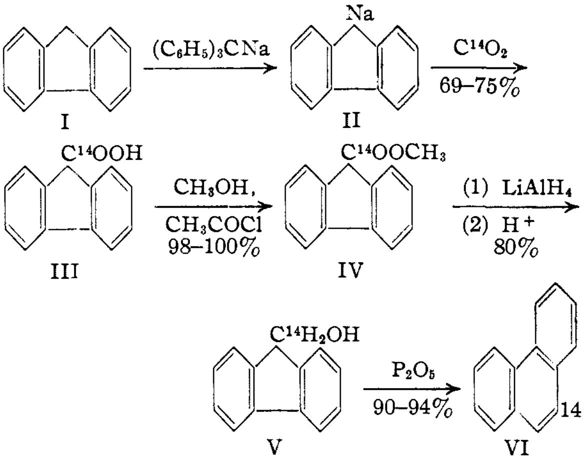
[CONTRIBUTION FROM THE OAK RIDGE NATIONAL LABORATORY]

The Synthesis of Phenanthrene-9-C^{14} (1,2)

BY CLAIR J. COLLINS

Due to the widespread interest in cancer producing substances, it appeared that a simple method for introducing carbon-14 in reasonable yields into aromatic polynuclear hydrocarbons should be of value. Accordingly, a synthesis of phenanthrene containing carbon-14 in the 9-position (VI) which the author has designated[3] phenanthrene-9-C^{14} has been effected by means of the Wagner rearrangement[4] of 9-fluorenemethannol-10-C^{14} (V). A new synthesis of the latter compound has been developed. Fluorene (I) was converted to 9-fluorenesodium (II) by interaction with triphenylmethylsodium. Carbonation with carbon dioxide-C^{14} yielded 9-fluorenecarboxylic acid-10-C^{14} (III). Reduction of the methyl ester (IV) with lithium aluminum hydride[5] produced 9-fluorenemethanol-10-C^{14} (V).



The complete synthesis was first worked out with non-radioactive materials, and each compound in the series was purified and characterized. The series was finally effected with purification only at the phenanthrene stage. The generality of this synthetic method is now under investigation.

Acknowledgment.—The author wishes to thank Professor Weldon G. Brown, of the University of Chicago, for the design of the extraction apparatus (Fig. 2) as well as for his many suggestions during the course of this work.

Experimental

Determination of Radioactivity.—Carbon-14 determinations were carried out by measuring the ionization current of carbon dioxide-C^{14} by means of a dynamic condenser electrometer.[6,7] The wet combustion method[8] of Van Slyke, Folch and Plazin was employed to oxidize 9-fluorenecarboxylic acid-10-C^{14} and phenanthrene-9-C^{14} (1-5 mg. samples). The carbon dioxide thus formed was collected in an ionization chamber which had previously been evacuated, using nitrogen to sweep the carbon dioxide into the chamber and to fill it to atmospheric pressure. Barium carbonate-C^{14} samples were similarly analyzed after decomposition with dilute perchloric acid. The conversion of the measured ionization currents to activities in millicuries was made on the basis of data obtained in this laboratory by Dr. W. B. Leslie employing similar chambers and a barium carbonate sample of known isotopic composition.

9-Fluorenecarboxylic Acid (III).[9]—The vacuum line shown in Fig. 1 was used for this preparation. In a typical run, 100 mg. of barium carbonate was weighed into flask A which could be placed directly on the balance pan. The apparatus was then swept with nitrogen. The exhaust nitrogen was passed through Drierite, a barium hydroxide bubbler and soda-lime. Decomposition of the barium carbonate was effected by addition of 5–8 cc. of 5 *M* perchloric acid. Next, nitrogen was passed through the system at a convenient rate for fifteen minutes. The cooling mixture surrounding the Dry Ice trap was kept at −50° to −55° by adjusting the amount of Dry Ice in the CHCl$_3$–CCl$_4$ mixture. This trap served to collect water vapor; when cooled to Dry Ice temperature, a significant amount of carbon dioxide was retained. Carbon dioxide was frozen in the liquid nitrogen trap. After fifteen minutes the acid decomposition mixture was heated gently with a free flame to liberate the last traces of carbon dioxide. In the reaction flask (B), 3.5 cc. of a stock triphenylmethyl sodium solution, prepared from 2.0 g. of sodium, 5.0 g. of triphenylchloromethane, 40 cc. of dry ether and 40 cc. of dry benzene, by the procedure of Bachmann and Wiselogle[10] was added to 150 mg. of fluorene (m. p. 114.0–114.5°)[11] and the flask was joined to the line. The entire operation was carried out under dry nitrogen. After stirring for three minutes, by means of a magnetic stirring bar, the color changed from deep red to light orange, and the mixture was frozen in liquid nitrogen. The two traps (b, c, Fig. 1) and the reaction flask (B) were evacuated to a pressure of less than 1 mm. of mercury. The carbon dioxide was then distilled from trap c into reaction flask B by cooling the latter with liquid nitrogen, and the flask was isolated from the rest of the line. Upon warming to a

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(2) Presented before the Division of Organic Chemistry at the 112th Meeting of the American Chemical Society, New York, N. Y., September 15, 1947.

(3) The carbon-14 labeled compounds described in this paper have been named by analogy to the rules set down in *Chemical Abstracts* (**39**, 5874-5875 (1945)) for deuterium and tritium. Since the prefix "deuterio" is not recommended for compounds containing deuterium, use of the term "radio" to denote the presence of carbon-14 has been avoided. Unlike deuterium nomenclature, however, the present author recommends the use of capital C in preference to lower case *c* for carbon-14 to avoid confusion with the lower case letters denoting bridgehead positions 4a, 4b, 8a, and 10a in phenanthrene. At tracer levels of C^{14} concentrations, "phenanthrene-9-C^{14}" and "phenanthrene-9,10-C$^{14}_2$" are indistinguishable because of the equivalence of the 9- and 10- positions. Pending the adoption of a formal convention the simpler designation has been used.

(4) Brown and Bluestein, THIS JOURNAL, **62**, 3256 (1940).

(5) Nystrom and Brown, *ibid.*, **69**, 1197 (1947); *ibid.*, **69**, 2548 (1947).

(6) Palevsky, Swank and Grenchik, *Rev. Sci. Instr.*, **18**, 298 (1947).

(7) Scherbatskoy, Gilmartin and Swift, *ibid.*, **18**, 415 (1947).

(8) Van Slyke, Folch and Plazin, *J. Biol. Chem.*, **136**, 509 (1940).

(9) Burtner and Cusic, THIS JOURNAL, **65**, 264 (1943)

(10) Bachmann and Wiselogle, *ibid.*, **58**, 1943 (1936).

(11) All melting points were determined on a Fisher–Johns melting point block.

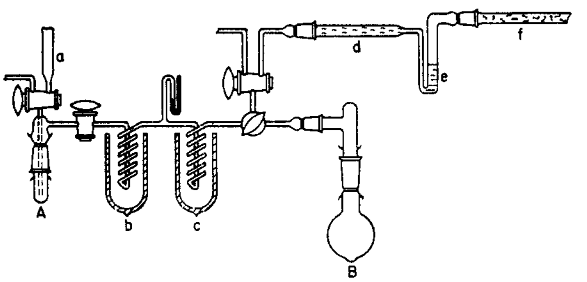

Fig. 1.—Carbonation apparatus: a, perchloric acid funnel; b, Dry Ice trap; c, liquid nitrogen trap; d, drierite; e, barium hydroxide solution; f, soda lime.

point at which the magnetic bar would just turn in the mixture, the reaction was complete, as indicated by a zero pressure in the system when the mixture was cooled to Dry Ice temperature. After admitting nitrogen, flask B was detached and 10 cc. of water was added to it. The layers were separated by means of the extraction apparatus shown in Fig. 2. The ether–benzene layer was washed twice with 5-cc. portions of water, and the combined aqueous layers were washed twice with 3-cc. portions of ether. Next, 10 cc. of 1 *N* hydrochloric acid was added to the aqueous layer, forming a white precipitate which was usually filtered directly when non-radioactive material was used. With radioactive material, however, the mixture was not filtered, but was treated with four 4-cc. portions of ether. The ether layer was washed once with 4 cc. of water, and then treated with three 4-cc. portions of saturated sodium bicarbonate solution. The bicarbonate layer, after one washing with 3 cc. of ether, was decomposed with 10 cc. of 6 *N* hydrochloric acid. Extraction with ether and concentration yielded 73–80 mg. of 9-fluorenecarboxylic acid (III); m. p. 222–226°. Consistent yields of 69–75% were obtained. The best yield was 86%.

Methyl 9-Fluorenecarboxylate (IV).—To 115.5 mg. of 9-fluorenecarboxylic acid (III) was added a chilled mixture of 5.0 cc. of methanol and 0.1 cc. of acetyl chloride. After standing at room temperature for one hour the contents of the flask were taken to dryness, yielding 120 mg. of methyl 9-fluorenecarboxylate (IV), m. p. 63.0–63.5°, 98%.

9-Fluorenemethanol (V).[12]—To 108 mg. of methyl 9-fluorenecarboxylate (IV) in 5.0 cc. of ether was added 10 cc. of 0.15 *M* lithium aluminum hydride solution (in ether). The mixture was stirred for ten minutes and then treated with 10 cc. of moist ether followed by 5.0 cc. of 6 *N* hydrochloric acid. The layers were separated, and the ether layer was washed with 5.0 cc. of water, and taken to dryness, yielding 82.4 mg. of crude alcohol melting at 80–85° (87%). One crystallization gave a product melting at 94–96°. The carbinol (7.7 mg.) was converted to 6.3 mg. (90%) of phenanthrene (VI) by the procedure of Brown and Bluestein.[4]

Phenanthrene-9-C^{14} (VI) **Synthesis from Barium Carbonate-C^{14}.**—The carbonation reaction was carried out as described elsewhere in this paper using 211.3 mg. of $BaC^{14}O_3$ containing 11.65 millicuries of carbon-14 per mole. Decomposition of this material produced 46.8 mg. of carbon dioxide-C^{14} (47.2 mg. theoretical) determined by direct weight in a gas weighing bulb. This was distilled into 9-fluorenesodium prepared from 300.0 mg. of fluorene and 7–8 cc. of triphenylmethylsodium solution.[10] The yield of 9-fluorenecarboxylic acid-10-C^{14} was 164.5 mg. (73%) whose activity was 11.62 millicuries carbon-14 per mole. To 122.0 mg. of this acid was added 5.0 cc. of methanol and 0.15 cc. of acetyl chloride. After standing for one hour at room temperature, the solution was concentrated in an air stream and desiccated to constant weight of 124.4 mg. over phosphorus pentoxide. This material was dissolved in 7 cc. of ether and to it was added 10 cc. of 0.16 molar lithium aluminum hydride solution. After stirring for fifteen minutes, 5 cc. of moist ether was added, followed by 5 cc. of 6 *N* hydrochloric acid. The layers were separated, the ether layer was washed with 5.0 cc. of water and taken to dryness and desiccated, yielding 114.8 mg. of an oil, which was dissolved in 10 ml. of xylene (doubly distilled over phosphorus pentoxide). To this solution was added 200–400 mg. of phosphorus pentoxide, and the mixture was heated under reflux for thirty minutes. After cooling, 5 cc. of water was added. The layers were separated and the xylene layer was washed twice with 5-cc. portions of water and concentrated and desiccated, yielding 170 mg. of an oil, which was transferred to a centrifuge tube fitted with a 19/38 female joint. This centrifuge tube was so designed that it could replace flask 1 of the extraction apparatus (Fig. 2). To this oil was added 60 mg. of picric acid and then 3.0 cc. of saturated ethanolic picric acid solution. The tube was heated with a free flame until a clear solution resulted; it was then allowed to cool. The phenanthrene picrate was separated by centrifuging, the supernatant liquid being drawn off using the extraction apparatus (Fig. 2). The picrate was decomposed with dilute aqueous sodium hydroxide solution, and extracted with ether, which was washed with water and concentrated. A repetition of this process with the solid so obtained yielded 72.5 mg. of phenanthrene-9-C^{14}, m. p. 94–95°; activity, 10.78 millicuries carbon-14 per mole. The over-all yield from barium carbonate was 51%. One crystallization from ethanol yielded white crystals melting at 96–97°. The picrate of this material melted at 141°. There was no depression of melting point when this material was mixed with an authentic sample of phenanthrene.

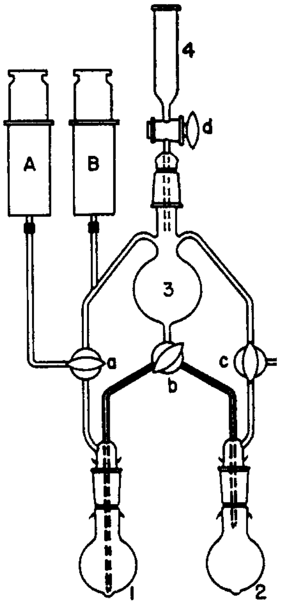

Fig. 2.—Extraction apparatus.

Extraction Procedure.—All extractions were carried out in the apparatus sketched in Fig. 2. The 50-cc. flasks 1 and 2 were interchangeable and were used in the carbonation apparatus (Fig. 1) as the reaction flask B and also in the lithium aluminum hydride reductions as the reactor vessels. This procedure prevented mechanical loss, and kept laboratory contamination with carbon-14 at a minimum. Chromatographic adsorptions were effected by replacing flask 2 (Fig. 2) with a chromatograph tube sealed to a 19/38 female glass joint.

The layers to be separated were placed in flask 1. By proper setting of the stopcocks, downward pressure on the plunger in cylinder A forced both layers into vessel 3 and also moved the plunger in cylinder B upward. Mixing was effected by pressing plunger A downward and forcing air through the two layers in 3. Solvents were added through 4, and by manipulation of stopcock b, liquid could be placed in flasks 1 and 2.

Summary

Fluorene (I) has been converted to 9-fluorenecarboxylic acid-10-C^{14} (III) by carbonation of 9-fluorenesodium (II) with carbon dioxide-C^{14}. Lithium aluminum hydride reduction of the methyl ester (IV) yielded 9-fluorenemethanol-10-

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[12] The reduction of the free acid (III) proceeds very slowly, and even after twenty-four hours approximately 10% of the starting material is recovered. Further, prolonged treatment of the acid with lithium aluminum hydride in ether solution decreases the yield of carbinol.

C^{14} (V). Dehydration of V with phosphorus pentoxide was accompanied by a Wagner rearrangement to form the desired phenanthrene-9-C^{14} (VI). The over-all yields of VI, based on barium carbonate, were 50–55%.

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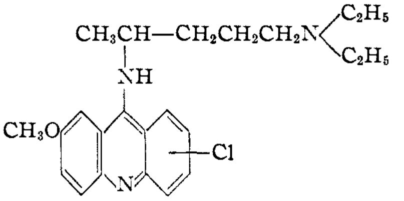
[CONTRIBUTION FROM THE CONVERSE MEMORIAL LABORATORY OF HARVARD UNIVERSITY]

The Synthesis of Nuclear Isomers of Quinacrine

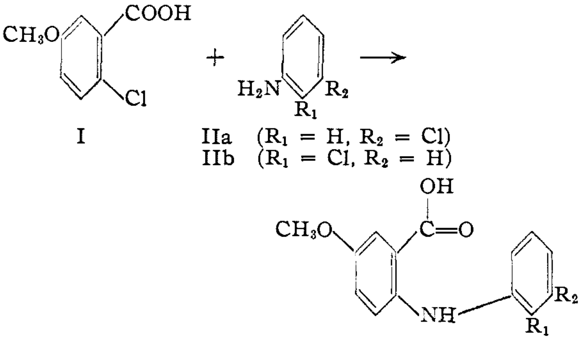
BY WILLIAM G. DAUBEN[1]

During the past few years much work has been done on the synthesis of compounds related to Quinacrine. However, of the four possible isomers of this compound which have the methoxyl



group in position two of the acridine nucleus and the chlorine atom in the opposite, nitrogen-free ring, only two have been reported. They are the 2-methoxy-6-chloro-9-substituted-aminoacridine[2] (Quinacrine) and the related 7-chloro isomer.[3] The present paper is concerned with the synthesis of the 5-chloro and the 8-chloro isomers.[4]

Following the observations of Ullmann and Kipper[5] that 2-chloro-5-methoxybenzoic acid[6] (I) can be used in the Ullmann condensation to prepare substituted N-phenylanthranilic acids (III), this compound (I) was utilized as the precursor of the desired methoxyl-substituted ring of the acridine. When the above acid (I) was allowed to react with *m*-chloroaniline (IIa) in the presence of anhydrous potassium carbonate and copper powder in boiling isoamyl alcohol, N-(3′-chlorophenyl)-5-methoxyanthranilic acid (IIIa) was formed in a yield of 19.9% and the majority of the starting acid (I) was recovered. Likewise, when acid I was allowed to react with *o*-chloroaniline (IIb), N-(2′-chlorophenyl)-5-methoxyanthranilic acid (IIIb) was isolated in a yield of only 11.4% and again the majority of the starting acid was recovered. It was found that the use of solvents with different boiling points, as *n*-butanol, *n*-pentanol, *n*-hexanol and cyclohexanol, gave still lower yields and that when the reaction was conducted in boiling nitrobenzene extensive decomposition occurred.



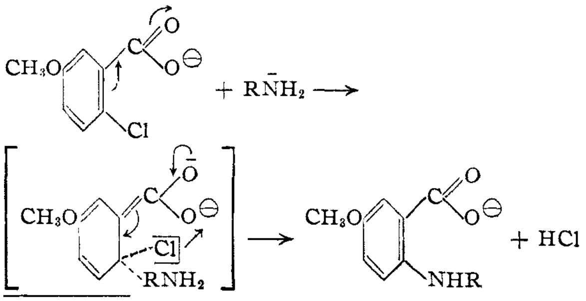
I

IIa $(R_1 = H, R_2 = Cl)$
IIb $(R_1 = Cl, R_2 = H)$

III $(R_1 = R_2 = H)$
IIIa $(R_1 = H, R_2 = Cl)$
IIIb $(R_1 = Cl, R_2 = H)$

The small quantity of the desired materials (IIIa and IIIb) was not easily separated from the large amount of starting acid by fractional crystallization. However, this mixture was easily separated by partial acidification of a solution of their potassium salts since a substituted-anthranilic acid is a much weaker acid than a substituted benzoic acid. Crude product was precipitated when the *p*H was adjusted to seven and the starting acid was deposited from solution at a *p*H of five.

In view of the poor yields obtained in the above condensations, it is interesting to note that Ullmann and Kipper[5] have reported that the same acid (I) reacts with aniline to give N-phenyl-5-methoxyanthranilic acid (III) in a yield of 80% and that Lehmstedt and Schrader[7] have reported



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[1] Present address: Department of Chemistry, University of California, Berkeley 4, California.

[2] Mauss, German Patents 553,072, 565,411.

[3] Feldman and Kopeliowitsch, *Arch. Pharm.*, **273**, 488 (1935).

[4] Since this paper was submitted for publication, Grigorovskii and Terent'eva (*J. Gen. Chem.* (*U. S. S. R.*), **17**, 517 (1947)) have reported the synthesis of the 5-chloro isomer and the attempted preparation of the 8-chloro isomer. The 2-methoxy-5,9-dichloroacridine (IV), prepared from 2,3-dichlorobenzoic acid and *p*-anisidine through the intermediate N-(4′-methoxyphenyl)-3-chloroanthranilic acid, had identical physical properties with the compound reported in this work. They, likewise, were unable to obtain a crystalline hydrochloride of the Quinacrine analog but they did obtain a solid oxalate. The 5-chloro isomer showed no anti-malarial activity. Their attempted synthesis of the 8-chloro isomer from 2,6-dichlorobenzoic acid and *p*-anisidine failed and the product isolated from the Ullmann reaction was *m*-bis-(*p*-methoxyanilino)-benzene.

[5] Ullmann and Kipper, *Ber.*, **38**, 2120 (1905).

[6] Peratoner and Condorelli, *Gazz. chim. ital.*, **28**, I, 213 (1898).

[7] Lehmstedt and Schrader, *Ber.*, **70**, 838 (1937).