CLXXI.—*The Synthesis of Complex Acridines.*

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THE researches during the past decade on the constitution of the morphine group of alkaloids lend peculiar interest to the study of the more complex heterocyclic compounds, especially of those derived from phenanthrene. The subject has already attracted the attention of chemists; thus Hinsberg and Garfunkel (*Annalen*, 1896, **292**, 264), J. Schmidt and Kämpf (*Ber.*, 1902, **35**, 3120), Calhane and Wheeler (*Amer. Chem. J.*, 1899, **22**, 457), and others have investigated *p*-diazines derived from phenanthrene; a phenanthroxazine has also been described by Bamberger and Grob (*Ber.*, 1901, **34**, 533), and quite recently Herschmann (*Ber.*, 1908, **41**, 1998) has succeeded in obtaining 9:10-phenanthraquinoline from 9-aminophenanthrene by Skraup's method. The experiments described in the present paper deal with acridines derived from

phenanthrene and from fluorene, which contains a triple ring system analogous to that of the former substance.

Complex acridines have been previously investigated by the present author, in conjunction with Prof. Senier (compare Senier and Austin, *Trans.*, 1906, **89**, 1387; 1907, **91**, 1233, 1240; 1908, **93**, 63), but the most complex derivatives examined were those of the phenonaphthacridines and of the dinaphthacridines. The methods devised for the preparation of these substances have now been utilised for the production of the acridines derived from phenanthrene and fluorene; these are:

(1). The condensation of an amine with methylene dihalides (Senier and Goodwin, *Trans.*, 1902, **81**, 280).

(2). The condensation of a mixture of an amine and α -naphthol with methylene dihalides (Senier and Austin, *Trans.*, 1907, **91**, 1240; Senier and Compton, *Trans.*, 1907, **91**, 1927).

In the case of phenophenanthracridine, another method has been applied, namely:

(3). The condensation of phenanthraquinone and *o*-nitrobenzyl chloride in presence of stannous chloride; this is an adaptation of Baezner's method (*Ber.*, 1904, **37**, 3077).

In applying the first of these methods to the production of diphenanthracridines, 9-aminophenanthrene was chosen as the most readily obtainable of the isomeric aminophenanthrenes. On condensing this substance in the usual manner with methylene di-iodide, a diphenanthracridine is formed, which, from the nature of the reaction, must have the structure (I).

The product of the third method of synthesis must be a phenophenanthracridine of the structure (II).

(I.)

(II.)

Turning to the acridines derived from fluorene, it is evident that on account of the structure of the amine employed, 2-amino-fluorene, there is room for doubt as to the constitution of the products, for when 2-amino-fluorene (III) is condensed with methylene dihalides the product may have either of the structures (IV) and (V).

Again starting with 2-aminofluorene (III), and submitting this to condensation with methylene di-iodide and α -naphthol, the fluorenenaphthacridine which is formed might be represented by either of the following formulæ, (VI) and (VII):

At present no definite evidence in favour of one or other of these formulæ can be adduced, but experiments are in progress to effect the fission of the methylene ring system in the fluorene nucleus of these substances, and it is hoped that by suitable treatment of the products, derivatives of acridine itself, with substituents in known positions, will be obtained.

1. Preparation of 9-Aminophenanthrene.

This compound has been prepared by J. Schmidt and Strobel (*Ber.*, 1901, **34**, 1461) from 9-nitrophenanthrene by reduction, and also by J. Schmidt and Ladner (*Ber.*, 1904, **37**, 3575) by the reduction of 10-bromo-9-nitrophenanthrene. The latter method is to be preferred, but the yield is still far from satisfactory. In this method of preparation several steps are involved; first, the direct addition of bromine to phenanthrene; secondly, the conversion of phenanthrene dibromide into monobromophenanthrene; thirdly, the nitration of the latter and the separation of pure 10-bromo-9-nitrophenanthrene from by-products; and lastly, the reduction of 10-bromo-9-nitrophenanthrene to 9-aminophenanthrene. Since useful modifications of the methods described in the literature have been introduced, during the present experiments, into each stage of the reaction, the process adopted is here described.

Bromination of Phenanthrene.—Various samples of commercial phenanthrene were first used, but the results were seldom satisfactory, owing to the presence of anthracene, which formed dibromoanthracene. The solvents formerly used were carbon disulphide and ether. Ether gives uncertain results, and the use of carbon disulphide in large quantity is both unpleasant and dangerous. Very good results were obtained by dissolving pure dry phenanthrene (1 mol.) in commercial carbon tetrachloride (dried with potassium carbonate), and adding to the cooled solution dry bromine (2 atoms), dissolved in the same solvent. The bromine was previously dried over sulphuric acid and distilled. In this way the fuming of the liquid, owing to the liberation of hydrogen bromide, was greatly reduced. The somewhat unstable phenanthrene dibromide soon crystallised as a yellow solid.

Preparation of 10-Bromophenanthrene.—The dibromide was immediately transferred to a beaker and melted by heating on the water-bath until the copious fumes of the hydrogen bromide ceased. 10-Bromophenanthrene remained as an oil, which solidified on cooling to a mass of crystals. The latter may be recrystallised from light petroleum. Thirty-two grams of phenanthrene gave 20 grams of bromophenanthrene.

Nitration of 10-Bromophenanthrene.—The nitration, as described by J. Schmidt, gives a mixture of 10-bromo-9-nitrophenanthrene and 3-nitrophenanthraquinone, which is not easily separated into its constituents. It is better to use a slight excess of the strongest fuming nitric acid. Instead of heating the mixture for twenty minutes, 10-bromophenanthrene was dissolved in hot glacial acetic acid containing a little acetic anhydride, a slight excess of nitric acid was added, and the mixture was cooled at once without further heating. A yellow solid separated, which, when freed from the mother liquor, was treated with boiling toluene and filtered from the undissolved residue. The latter proved to be 3-nitrophenanthraquinone. From the filtrate a yellow solid crystallised, which melted at about 195°. Further fractionation gave no purer product. Eventually a very pure specimen of 10-bromo-9-nitrophenanthrene was obtained by the following method, which was indicated in the investigation of the action of various reducing reagents on it. The impure 10-bromo-9-nitrophenanthrene was suspended in methylated spirit containing a little stannous chloride in solution. The liquid immediately became red. It was boiled for about two hours under a reflux condenser. The main portion of the solid remained undissolved, but the solution became paler. On cooling, the liquid was filtered off, and the residue recrystallised from benzene. Pale yellow crystals of 10-bromo-9-nitro-

phenanthrene were obtained, melting at 209°. The yield was, however, small.

Reduction of 10-Bromo-9-nitrophenanthrene.—J. Schmidt's method of reduction by using stannous chloride and glacial acetic acid gave very poor results. Other reducing agents, such as sodium and iron, were used, without obtaining the desired result. With zinc dust and ammonia, however, the substance was found to be reduced easily. Five grams of 10-bromo-9-nitrophenanthrene were suspended in about 200 c.c. of methylated spirit, and 12 grams of zinc dust were added. The mixture was heated for about four hours on the water-bath under a reflux condenser. At short intervals a few c.c. of concentrated ammonia were added, until about 40 c.c. altogether had been used. The hot red liquid was filtered from the solid, evaporated to a small bulk, and diluted with water. A white solid separated, which was collected, dried, and recrystallised from light petroleum, in which it is only sparingly soluble. Long, straw-coloured needles, turning darker in the air and melting sharply at 138°, were obtained. They were identical with 9-aminophenanthrene described by J. Schmidt.

2. Condensation of 9-Aminophenanthrene and Methylene Dihalides:

Methylene dichloride was first used. This was found to react at a high temperature in sealed tubes. A dark brown powder, having a very high melting point, was obtained, and the yield was extremely poor. With methylene diiodide, however, a satisfactory result was obtained. Equimolecular proportions of methylene diiodide and 9-aminophenanthrene were heated together in a test-tube in an oil-bath. When the temperature of the bath reached 150°, the contents of the test-tube suddenly solidified, and the heating was discontinued. On treating the substance with alcoholic potash to remove halogen, and with acetone to remove any oily impurity, a pale yellow solid was obtained, which could be recrystallised from nitrobenzene. It is practically insoluble in the usual organic solvents, and does not melt below 320°. It was necessary to distil the solid under diminished pressure in order to obtain it sufficiently pure for analysis. It distils easily and without much decomposition:

0.1235 gave 0.4138 CO₂ and 0.0540 H₂O. C=91.38; H=4.85.

C₂₉H₁₇N requires C=91.82; H=4.48 per cent.

3. *Condensation of Phenanthraquinone and o-Nitrobenzyl Chloride in presence of Stannous Chloride: Phenophenanthracridine,*

Four grams of phenanthraquinone were suspended in about 30 c.c. of boiling methylated spirit containing 30 grams of stannous chloride in solution. Twenty c.c. of concentrated hydrochloric acid were gradually added, and the liquid was boiled until no undissolved residue was left. During the latter process the solution became almost black. Three grams of *o*-nitrobenzyl chloride were added carefully in very small portions, and the heating was continued on the water-bath for five or ten minutes. Even at this temperature a dark brown solid separated. When cold, the mixture was filtered, and the solid residue was washed with methylated spirit and then once with a little cold acetone. The solid was then treated with boiling concentrated aqueous potassium hydroxide, which produced a yellow colour. Cold water was added, and the alkaline liquid was filtered off. The residue was well washed with cold water, and with a little acetone, to remove any black impurity still remaining. About 5 grams of a yellow powder were obtained in this way. The substance was recrystallised from benzene, from which it separated in bright yellow needles, melting at 204°. Analyses showed that it was not quite pure, but, on distilling it under diminished pressure and recrystallising again from benzene, satisfactory results were obtained. The melting point remained unaltered. Solutions in benzene, toluene, or glacial acetic acid are fluorescent:

0.1317 gave 0.4350 CO₂ and 0.0581 H₂O. C = 90.08; H = 4.90.

C₂₁H₁₃N requires C = 90.32; H = 4.66 per cent.

The compound is therefore a *phenophenanthracridine*.

4. *Preparation of 2-Aminofluorene.*

Diels prepared 2-aminofluorene (*Ber.*, 1901, **34**, 1759) by nitrating fluorene and reducing the nitro-compound with zinc dust and calcium chloride, but it is more convenient to reduce the nitrofluorene with stannous chloride. Ten grams of finely-ground 2-nitrofluorene were suspended in 100 c.c. of methylated spirit. Thirty-five grams of stannous chloride were added, and the mixture was boiled under a reflux condenser until a clear solution was obtained, after which about 25 c.c. of concentrated hydrochloric acid were gradually added, and the boiling continued for about three hours. The addition of hydrochloric acid caused a white

precipitate to form, which, however, slowly dissolved. On cooling the liquid, a white double salt separated. This was collected, treated with excess of boiling aqueous sodium hydroxide, and then again collected. The residue was extracted two or three times with boiling methylated spirit, and filtered from an insoluble residue. On cooling the filtrates, white needles of 2-aminofluorene, melting at 129°, separated. They could be further purified by recrystallisation from benzene.

5. Condensation of 2-Aminofluorene with Methylene Dihalides.

2-Aminofluorene reacted with methylene dichloride in a sealed tube heated to 250°. A non-crystallisable, brown powder was obtained, which did not melt below 300°, and which could not be purified by recrystallisation nor by distillation. Methylene diiodide, however, reacts very energetically with 2-aminofluorene when heated. The two substances were warmed together in a test-tube immersed in an oil-bath, when it was found that the reaction began at about 120°. The contents of the tube were treated in the same manner as in the case of the corresponding experiment with 9-aminophenanthrene, but the product could not be purified. On distillation under reduced pressure, it decomposed, and no suitable solvent could be found from which to recrystallise it. It was therefore not analysed. It was insoluble in water, alcohol or light petroleum; sparingly soluble in boiling acetone or in boiling ethyl acetate, with slight fluorescence, and readily so in benzene, toluene or cold pyridine.

6. Condensation of a Mixture of 2-Aminofluorene and α -Naphthol with

Methylene Di-iodide: Fluorene- $\overset{\text{N-}\alpha}{\underset{\text{CH-}\beta}{|}}$ -naphthacridine,

This reaction is much more easily controlled than that between methylene di-iodide and 2-aminofluorene alone. Equimolecular proportions of α -naphthol and 2-aminofluorene were heated together in an open test-tube in an oil-bath. One molecular proportion of methylene di-iodide was then added, when it was found that the contents of the tube solidified at about 148°. As soon as this occurred, heating was discontinued, and the contents of the tube were treated with boiling methylated spirit until almost the whole of the substance was dissolved. Excess of aqueous potassium hydroxide was added to the solution, when a solid separated. The latter was collected, washed with water and acetone, dried,

distilled under reduced pressure, and recrystallised two or three times from toluene. Yellow needles, melting at 259° , were obtained, which, on analysis, proved to be *fluorene*- $\overset{\text{N-}\alpha}{\underset{\text{CH-}\beta}{|}}$ -*naphthacridine*.

Great care had to be taken during the analysis to avoid an incomplete combustion of the carbon:

0.1076 gave 0.3584 CO_2 and 0.0495 H_2O . $\text{C}=90.84$; $\text{H}=5.11$.

$\text{C}_{24}\text{H}_{15}\text{N}$ requires $\text{C}=90.85$; $\text{H}=4.73$ per cent.

In conclusion, I desire to express my thanks to Prof. Collie and to Assistant-Prof. Smiles for much valuable advice during the course of this investigation.

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