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Potential Leukopenia-Inducing Amines. I. 6-Amino-12-ethylchrysene

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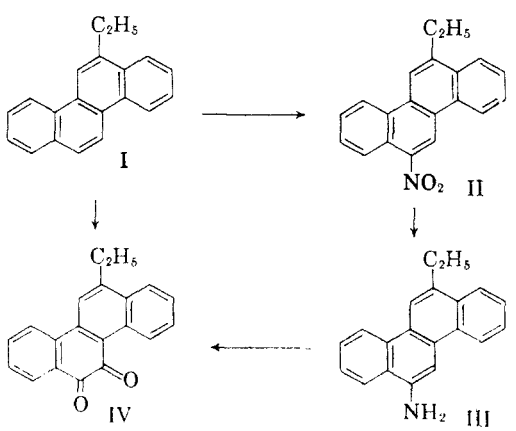
Received August 10, 1959

6-Amino-12-ethylchrysene has been synthesized by two different methods, both starting from 6-ethylchrysene, and the structure of this amine has been determined. This work establishes the orientation of substituents in the nitration and Friedel-Crafts reactions of a 6-alkylchrysene.

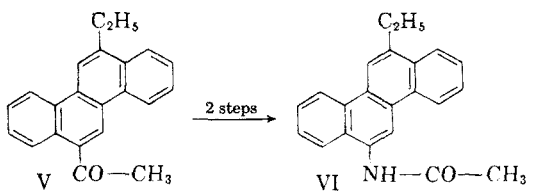
6-Aminochrysene is known to be a leukopenia-promoting agent with a pronounced atrophying effect on the spleen.[1] Experimentally, it inhibits the growth of spontaneous adenocarcinoma of the breast[2] and retards the development of L 1210 leukemia[3] in mice. These considerations prompted the search for compounds possessing similar biological activities, and particularly those which would have greater lipoid solubility than 6-aminochrysene itself. In the latter respect, alkyl homologs of 6-aminochrysene appeared promising, and 12-ethyl-6-aminochrysene (III) was therefore prepared, by two different methods.

First method. 6-Ethylchrysene (I), easily prepared by Wolff-Kishner reaction of 6-acetylchrysene, underwent reaction with nitric acid in mild conditions, to give a monosubstitution product, 12-ethyl-6-nitrochrysene (II); this was readily reduced by sodium hydrosulfite in ethanol medium to 6-amino-12-ethylchrysene, whose structure was established by oxidation with sodium bichromate in acetic acid medium to 12-ethylchrysene-5,6-quinone (IV), a compound that could also be obtained



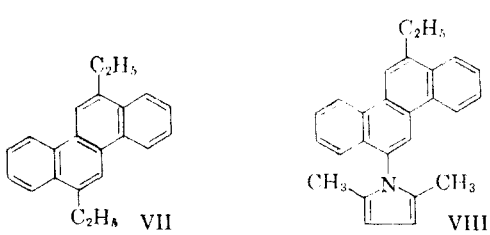
by direct oxidation of 6-ethylchrysene with the same reagent. From the standpoint of pure organic chemistry, this experiment demonstrates the greater resistance to oxidation of an alkylated *meso*-phenanthrene zone as compared with a non-substituted region.

Second method. The Friedel-Crafts acetylation of 6-ethylchrysene (a reaction which was shown by Funke and Ristic[4] to yield an acetyl-6-ethylchrysene whose structure they did not investigate) afforded 6-acetyl-12-ethylchrysene (V), as was proven by the Beckmann rearrangement of its oxime to 6-acetamino-12-ethylchrysene (VI), identical with the



product from the acetylation of the amine obtained by the first method. As it is known that the positions 5 and 11 in chrysene resist substitution because of particularly strong steric encumbrance at those two sites,[5] this second experiment establishes the orientation of substituents in Friedel-Crafts acylations of 6-alkylchrysenes. Hence, the 6,x-diethylchrysene prepared by Funke and Ristic by a Clemmensen reduction of the acetylation product of 6-ethylchrysene,[4] was 6,12-diethylchrysene (VII), which we now prepared in excellent yield by the Wolff-Kishner method.

As was to be expected, 6-amino-12-ethylchrysene has a considerably lower melting point than 6-aminochrysene, and is also far more soluble in lipoids. Its condensation with hexane-2,5-dione[6] readily yielded 6-(2,5-dimethyl-1-pyrryl)-12-ethylchrysene (VIII).



The results of biological studies will be reported at a later date.

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EXPERIMENTAL

Preparation of 6-acetylchrysene. The preparation of 6-acetylchrysene has frequently been reported in the literature,[7] the most satisfactory method being that of Carruthers,[8] where the use of methylene chloride as solvent ensures a smoother reaction than with carbon disulfide. So as to enhance the yield and to obtain an isomer-free ketone, we modified Carruthers' technique as follows. To a stirred mixture of 80 g. of aluminum chloride and 40 ml. of acetyl chloride in 2 l. of methylene chloride, 100 g. of chrysene (suspended in 700 ml. of methylene chloride) was added portionwise during 45 min. at a temperature ranging from 3° to 9°, and the mixture was then stirred for 3 hr. at room temperature. It was then refluxed for 2 hr., left to stand overnight at room temperature, then refluxed again for 1.5 hr. After decomposition with ice and hydrochloric acid, the methylene chloride solution was washed with 5% aqueous sodium hydroxide, then with water, dried over sodium sulfate, and the solvent removed by distillation. Crystallization of the residue from acetone afforded 95 g. of 6-acetylchrysene, lemon yellow needles, m.p. 144°.

Preparation of 6-ethylchrysene. A mixture of 54 g. of 6-acetylchrysene, 50 g. of 98% hydrazine hydrate, and 40 g. of potassium hydroxide in 1250 ml. of diethylene glycol was gently refluxed for 13 hr. with removal of water. When cooled, water was added, then dilute hydrochloric acid, and the solid precipitate was collected and recrystallized from ethanol-acetone. Yield: 47 g. (91.6%) of colorless needles, m.p. 129–130°; lit.[9] m.p. 126°.

12-Ethyl-6-nitrochrysene (II). To a suspension of 20 g. of ethylchrysene in 750 ml. of acetic acid, 16.5 ml. of fuming nitric acid (d = 1.49; dissolved in 250 ml. of acetic acid) was added at 33–35° with stirring. Within 5 to 10 min. a yellow precipitate had formed, and after 30 min. cooling in an iced water-bath, this was collected, washed with acetic acid, and recrystallized from 1 l. of acetone. Yield: 14.5 g. (61.7%) of silky pale yellow needles, m.p. 203°.

Anal. Calcd. for $C_{20}H_{15}NO_2$: C, 79.7; H, 5.0; N, 4.7. Found: C, 79.5; H, 5.0; N, 4.8. From the mother liquors of recrystallization of the nitro compound was isolated 2.2 g. of a product which crystallized from ethanol in shiny colorless leaflets, m.p. 184°, giving a blue coloration in sulfuric acid. The constitution of this byproduct is unknown.

12-Ethyl-6-aminochrysene (III). To a solution of 0.5 g. of the foregoing nitro-derivative in 400 ml. of hot ethanol, 1 g. of sodium hydrosulfite (dissolved in a few ml. of water) was added with stirring. Discoloration occurred, and after 15 min. a mineral precipitate was filtered off and the filtrate diluted with water, giving the amine which was washed with water, dried, and recrystallized twice from hexane, to yield 0.3 g. of cream-colored needles, m.p. 159° (the solvated product melted partly at 140–144°). The solution in ethanol gave an intense blue fluorescence.

Anal. Calcd. for $C_{20}H_{17}N$: C, 88.5; H, 6.3; N, 5.2. Found: C, 88.7; H, 6.3; N, 5.2.

6-Acetyl-12-ethylchrysene (V). To a solution of 24 g. of 6-ethylchrysene and 120 ml. of acetyl chloride in 400 ml. of dry carbon disulfide, 24 g. of finely powdered aluminum chloride was added, with stirring, during 15 min. and at room temperature. The mixture was left to stand for 13 hr., then refluxed for 5 hr. After decomposition with ice and hydrochloric acid, the solvent was distilled, and the solid precipitate was collected. This was treated with 80 ml. of acetone (for removal of the resins), and left overnight in the refrigerator, after which the crystalline mass that had formed was collected and recrystallized from ethanol (800 ml.), to give pale yellow needles, m.p. 131–132°. Evaporation of the acetonic mother liquors and crystallization of the residue from ethanol gave a further crop of the same ketone (total yield: 14.4 g.). Funke and Ristic[4] gave m.p. 131° for their product.

The corresponding *oxime*, prepared by heating for 24 hr. a mixture of 11 g. of the above ketone, 5.2 g. of hydroxylamine hydrochloride, and 2.2 g. of sodium hydroxide in 800 ml. of ethanol, crystallized from ethanol-benzene in beige needles (9.7 g.), m.p. 218–219°.

Anal. Calcd. for $C_{22}H_{19}NO$: C, 84.3; H, 6.1; N, 4.5. Found: C, 84.2; H, 6.3; N, 4.5.

6-Acetamino-12-ethylchrysene (VI). Into a suspension of 9.4 g. of the foregoing oxime in 500 ml. of anhydrous ether and 50 ml. of benzene, was shaken, at room temperature and in small portions, 10 g. of finely powdered phosphorus pentachloride. Shaking was continued for 1.5 hr., by which time the oxime had undergone complete dissolution and rearrangement. After decomposition with ice and evaporation of the solvent, the precipitate obtained was recrystallized from toluene, yielding 3.5 g. of *12-ethyl-6-acetaminochrysene*, as colorless needles, m.p. 249°, which could be sublimed.

Anal. Calcd. for $C_{22}H_{19}NO$: C, 84.3; H, 6.1; N, 4.5. Found: C, 84.4; H, 6.2; N, 4.7.

A solution of 1.3 g. of this compound in a mixture of 300 ml. of ethanol and 100 ml. of hydrochloric acid was heated at reflux for 1 hr., and the solution was concentrated until a precipitate began to form. After 2 hr. in the refrigerator, the precipitate of *12-ethyl-6-aminochrysene hydrochloride* was collected, washed with ethanol and benzene, and dried; it melted at 200–203°, with decomposition above 175°. Treatment with potassium hydroxide in ethanol yielded the free *base*, m.p. 159° after crystallization from benzene; the melting point was not depressed on admixture with a sample prepared by reduction of 12-ethyl-6-nitrochrysene.

12-Ethylchrysene-5,6-quinone (IV). A suspension of 1 g. of 12-ethyl-6-acetaminochrysene in 15 ml. of acetic acid was refluxed for 30 min. with 4 g. of sodium bichromate. After cooling and dilution with water, the precipitate formed was collected, washed with water, and recrystallized from acetic acid, to furnish 0.7 g. of orange-red needles, m.p. 183–184° (the solvated product melted partly at 175–176°), giving a blue-violet coloration in sulfuric acid.

Anal. Calcd. for $C_{20}H_{14}O_2$: C, 83.9; H, 4.9. Found: C, 83.7; H, 4.8.

The same compound was obtained by oxidation of the free amine, or, with a lower yield, of 6-ethylchrysene.

The corresponding *phenazine*, prepared with *o*-phenylenediamine in acetic acid, crystallized from acetic acid in yellowish leaflets, m.p. 204–205°, giving an olive green coloration in sulfuric acid.

Anal. Calcd. for $C_{26}H_{18}N_2$: C, 87.1; H, 5.1; N, 7.8. Found: C, 87.0; H, 5.3; N, 7.9.

6-(2,5-Dimethyl-1-pyrryl)-12-ethylchrysene (VIII). A mixture of 0.3 g. of 12-ethyl-6-aminochrysene and 1 g. of hexane-2,5-dione was refluxed for 15 min. The solid obtained on cooling crystallized from ethanol after treatment with charcoal, to give shiny colorless needles (0.2 g.), m.p. 174–175°.

Anal. Calcd. for $C_{26}H_{23}N$: C, 89.4; H, 6.6. Found: C, 89.3; H, 6.8.

6,12-Diethylchrysene (VII). This *hydrocarbon*, prepared from 0.7 g. of 12-ethyl-6-acetylchrysene, 0.7 g. of hydrazine hydrate, and 0.7 g. of potassium hydroxide in 30 ml. of diethylene glycol, crystallized from ethanol in colorless leaflets (0.4 g.), m.p. 152°; lit.,[4] m.p. 145°.

Acknowledgment. This work was conducted with the financial aid of The Anna Fuller Fund, New Haven, Connecticut; the authors express their gratitude to Professor William U. Gardner and the Trustees of the Fund.

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