[CONTRIBUTION FROM THE DEPARTMENT OF ORGANIC CHEMISTRY, RADIUM INSTITUTE, UNIVERSITY OF PARIS]

SOME FEATURES OF THE CHEMISTRY OF 6-AMINOCHRYSENE

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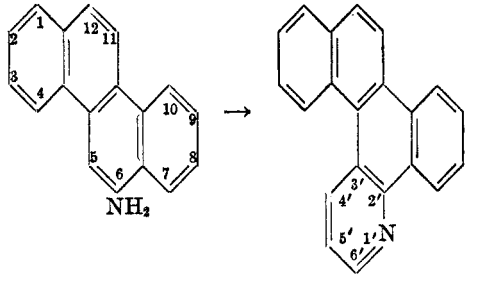
6-Aminochrysene (I), discovered simultaneously in 1890 by Abegg (1), and Bamberger and Burgdorf (2), has of late been mentioned in several patents (3) and by Newman and Cathcart (4). It has recently acquired biological importance as a chemical inhibitor of the growth of spontaneous adenocarcinoma of the breast, as well as of chemical carcinogenesis induced by 20-methylcholanthrene in mice; it produces an important atrophy of the spleen and of the hematopoietic system, suggestive of possible action in leukemia (5). In view of these biological findings, the chemistry of this amine has been more thoroughly investigated, and several of its derivatives prepared.

The Skraup condensation performed on 6-aminochrysene gave a moderate yield of 3′,2′-5,6-pyridinochrysene (II), a substance whose remarkably low melt-



I II

ing point is reminiscent of that of the parent carcinogenic hydrocarbon, 1,2-3,4-dibenzophenanthrene (6). Condensation of 6-aminochrysene with aromatic aldehydes in ethanol yielded the expected 6-arylideneaminochrysenes; reaction with acid chlorides in pyridine (7) afforded a series of 6-acetylaminochrysenes listed in Table I along with sulfonamides obtained from chlorides of arylsulfonic acids. A convenient alternative method for the preparation of 6-acetylamino- and 6-propionylamino-chrysene was the Beckmann rearrangement of the oximes of the readily accessible 6-acetyl- and 6-propionyl-chrysene. Bromination of 6-acetylaminochrysenes in cold acetic acid medium (because of the low solubility of the 6-acetylamino derivative, 6-*n*-butyrylaminochrysene was preferred for this reaction) afforded monobromo derivatives which, by analogy with the proven 6-position of attack in monosubstitution in chrysene (4, 8), should be 6-acylamino-12-bromochrysenes. This constitution was proven by chromic acid oxidation of 6-amino-12-bromochrysene (III), obtained on hydrolysis of these amides, to 12-bromo-5, 6-chrysenequinone (V), prepared by Funke and Ristic in another way (9). It should be mentioned that Abegg (1) obtained on treatment of his impure 6-acetylaminochrysene (m.p. 285°) with bromine in water, a bromo derivative described as shrinking at 180° and decomposing above 215°, whereas

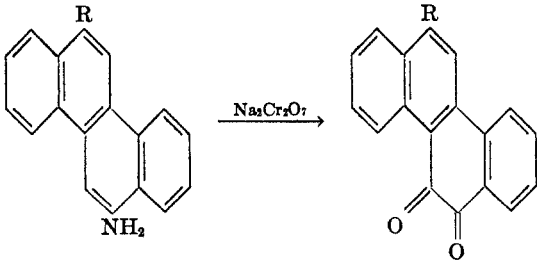
TABLE I

6-ACYLAMINOCHRYSENES AND 6-ARYLSULFONYLAMINOCHRYSENES

SUBSTITUENT	FORMULA	M.P., °C.	ANALYSES			
			Calc'd		Found	
			C	H	C	H
6-Formylamino[a]	$C_{19}H_{13}NO$	285	84.1	4.8	84.0	5.0
6-Propionylamino	$C_{21}H_{17}NO$	248	84.3	5.7	84.2	5.7
6-*n*-Valerylamino	$C_{23}H_{21}NO$	206	84.4	6.4	84.1	6.5
6-*n*-Hexanoylamino	$C_{24}H_{23}NO$	196	84.5	6.7	84.3	6.6
6-*n*-Heptanoylamino	$C_{25}H_{25}NO$	199	84.5	7.0	84.2	7.2
6-*n*-Nonoylamino	$C_{27}H_{29}NO$	176	84.6	7.6	84.5	7.6
6-*n*-Decanoylamino	$C_{28}H_{31}NO$	175–176	84.6	7.8	84.3	7.9
6-*n*-Undecanoylamino	$C_{29}H_{33}NO$	177–178	84.7	8.0	84.5	8.1
6-*n*-Dodecanoylamino	$C_{30}H_{35}NO$	168–169	84.7	8.2	84.6	8.4
6-Phenacetylamino	$C_{26}H_{19}NO$	269	86.4	5.3	86.2	5.5
6-(4-Isopropylbenzoyl)amino	$C_{28}H_{23}NO$	239	86.4	5.9	86.3	5.8
6-(α-Naphthoyl)amino	$C_{29}H_{19}NO$	256	87.7	4.8	87.4	5.0
6-(4-Xenoyl)amino	$C_{31}H_{21}NO$	296	87.9	5.0	88.0	5.1
6-(2-Thenoyl)amino	$C_{23}H_{15}NOS$	228	78.2	4.2	78.0	4.3
6-Benzenesulfonylamino[b]	$C_{24}H_{17}NO_2S$	228	75.2	4.4	75.3	4.4
6-(*p*-Chlorobenzenesulfonyl)amino	$C_{24}H_{16}ClNO_2S$	227	69.0	3.8	69.0	4.0
6-(*p*-Bromobenzenesulfonyl)amino	$C_{24}H_{16}BrNO_2S$	245	62.3	3.5	62.0	3.5
12-Bromo-6-*n*-heptanoylamino	$C_{25}H_{24}BrNO$	240	69.1	5.5	69.1	5.6
12-Bromo-6-*n*-nonoylamino	$C_{27}H_{28}BrNO$	215–216	70.1	6.1	70.3	6.1
12-Bromo-6-*n*-decanoylamino	$C_{28}H_{30}BrNO$	214–215	70.6	6.3	70.3	6.1

[a] Prepared by refluxing for 6 hours a solution of 1 g. of the amine in 20 g. of 98% formic acid, and recrystallizing the reaction product from acetic acid. [b] The sulfonamides were prepared from the corresponding sulfochlorides in pyridine solution.

the pure 12-bromo-6-acetylaminochrysene now prepared had m.p. 309–310°. Chlorination of 6-acetylaminochrysene and subsequent hydrolysis gave 6-amino-12-chlorochrysene (IV), identical with the reduction product of 12-chloro-6-nitrochrysene (10), and giving 12-chloro-5, 6-chrysenequinone (VI) on oxidation

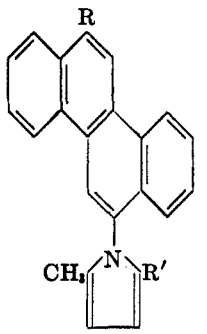


III R = Br
IV R = Cl

V R = Br
VI R = Cl

with sodium dichromate. 6-Aminochrysene readily underwent Knorr-Paal condensations (11) with γ-diketones; 6-(2, 5-dimethyl-1-pyrryl)chrysene (VII) was

thus obtained from acetonylacetone, and 6-(2-methyl-5-*n*-butyl-1-pyrryl)chrysene (VIII) from nonane-2, 5-dione.



VII R = H, R′ = CH_3
VIII R = H, R′ = *n*-C_4H_9

Several substances described in this paper are now undergoing biological tests for leukopenia-producing properties.

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EXPERIMENTAL

6-Acetylaminochrysene. (*a*) *From 6-aminochrysene.* To an ice-cooled solution of 25 g. of 6-aminochrysene [prepared from 6-nitrochrysene according to the Newman and Cathcart procedure (4)] in 200 g. of dry pyridine, 8 g. of acetyl chloride was added dropwise with stirring; the reaction mixture was poured into dilute hydrochloric acid, and the solid obtained was collected, washed with water, and recrystallized from acetic acid (charcoal). Yield, 28 g. (98%) of an almost colorless product, m.p. 301°; Newman and Cathcart (4) gave m.p. 299.5–301°.

(*b*) *From 6-acetylchrysene.* 6-Acetylchrysene, prepared in almost theoretical yield according to Funke and Müller (12), was converted in the usual way to its *oxime*, which crystallized from a mixture of ethanol and benzene in fine colorless prisms, m.p. 197–198°.

Anal. Calc'd for $C_{20}H_{15}NO$: C, 84.2; H, 5.3.
Found: C, 84.0; H, 5.3.

An ethereal solution of this oxime (1 mole) was shaken for 10 minutes with finely powdered phosphorus pentachloride (1 mole), and the reaction product was poured on ice; the solid obtained after evaporation of ether gave on recrystallization from acetic acid a 96% yield of 6-acetylaminochrysene, m.p. 301°.

6-Propionylchrysene. To a solution of 7 g. of chrysene and 35 ml. of propionyl chloride in 200 ml. of carbon disulfide, 8 g. of aluminum chloride was added portion-wise; the orange-red mixture was kept for 12 hours at room temperature with occasional shaking, decomposed with water, and the *ketone* obtained was purified by vacuum-distillation; it crystallized from ethanol in colorless needles, m.p. 127°; yield, 5 g. (57%). The constitution of this ketone was established by the identity of the product of Beckmann rearrangement of its oxime with 6-propionylaminochrysene, m.p. 248°, prepared from 6-aminochrysene.

Anal. Calc'd for $C_{21}H_{16}O$: C, 88.7; H, 5.6.
Found: C, 88.6; H, 5.8.

3′,2′-5,6-Pyridinochrysene (II). A mixture of 30 g. of 6-aminochrysene, 30 ml. of nitrobenzene, 60 g. of glycerol, and 6 g. of ferrous sulfate (13) was gently refluxed for 30 minutes, then kept at 145° for 4 hours. After dilution with water, and steam-distillation of the nitrobenzene, the hot solution obtained was filtered from a resinous solid (A) and concentrated; the 3′,2′-5,6-pyridinochrysene sulfate which crystallized on cooling gave on treatment with

aqueous ammonia the free *base* (3 g.), crystallizing from toluene in shiny yellowish leaflets, m.p. 126°; the m.p. given for 1,2-3,4-dibenzophenanthrene is 115° (6). The portion (A) was identified by m.p. and analysis is chrysene.

Anal. Calc'd for $C_{21}H_{13}N$: C, 90.3; H, 4.7; N, 5.0.
Found: C, 89.9; H, 4.8; N, 5.2.

The corresponding *picrate* crystallized from nitrobenzene as orange-yellow prisms, m.p. 242–243° (decomp. above 230°).

12-Bromo-6-acetylaminochrysene. To a solution of 2.9 g. of 6-acetylaminochrysene in cold acetic acid, 1.6 g. of bromine (in acetic acid solution) was added portion-wise with stirring; the solid obtained on dilution with water was collected, washed with water, and recrystallized from acetic acid, giving 3.2 g. (88% yield) of a single bromo derivative in sublimable, colorless needles, m.p. 309–310°.

Anal. Calc'd for $C_{20}H_{14}BrNO$: C, 65.9; H, 3.8.
Found: C, 65.8; H, 3.7.

12-Bromo-6-n-butyrylaminochrysene. Prepared from *n*-butyryl chloride, it crystallized from acetic acid in fine colorless needles, m.p. 285°; yield: 95%.

Anal. Calc'd for $C_{22}H_{18}BrNO$: C, 67.3; H, 4.6.
Found: C, 67.0; H, 4.6.

12-Bromo-6-aminochrysene (III). Three grams of the foregoing amide was heated for 12 hours with 50 ml. of a 20% solution of potassium hydroxide in ethanol; the solid obtained on dilution with water crystallized from ethanol in shiny yellowish prisms, m.p. 222° (decomp.); yield: 85%.

Anal. Calc'd for $C_{18}H_{12}BrN$: C, 67.1; H, 3.7.
Found: C, 67.0; H, 3.8.

In a patent, Neresheimer, Vollmann, and Zell (10) mentioned that they obtained by bromination of 6-aminochrysene a bromo amine, m.p. 220° (N-acetyl derivative m.p. 305°), which was believed to be different from 12-bromo-6-aminochrysene prepared by reduction of the corresponding nitro compound, and for which they found m.p. 262°.

12-Bromo-5,6-chrysenequinone (V). A solution of 1 g. of the foregoing amine in 50 ml. of acetic acid was refluxed with 5 g. of sodium dichromate for 8 hours; after filtration and dilution with water, a precipitate was obtained, which gave on recrystallization from acetic acid bright red prisms, m.p. 251°, giving a deep violet coloration with sulfuric acid; the *quinoxaline* obtained with *o*-phenylenediamine crystallized from nitrobenzene in silky yellow needles, m.p. 253°; Funke and Ristic (9) gave m.p. 249–250° for the quinone, and 252° for the quinoxaline. Yield of oxidation: 80%.

The *methylquinoxaline* (a mixture of isomers), prepared from 3,4-diaminotoluene, crystallized from acetic acid in bright yellow needles, melting at about 230°.

Anal. Calc'd for $C_{25}H_{15}BrN_2$: N, 6.6. Found: N, 6.5.

6-Amino-12-chlorochrysene (IV). A solution of 3 g. of 6-acetylaminochrysene in cold acetic acid was treated with 0.8 g. of chlorine (in acetic acid); the precipitate of *6-acetylamino-12-chlorochrysene* obtained on dilution with water was recrystallized twice from acetic acid, giving fine colorless needles, m.p. 288–289°; yield: 2 g. (61%).

Anal. Calc'd for $C_{20}H_{14}ClNO$: C, 75.1; H, 4.4.
Found: C, 74.9; H, 4.3.

This amide gave on hydrolysis with potassium hydroxide in ethanol *6-amino-12-chlorochrysene*, crystallizing from ethanol in yellowish prisms, m.p. 214–215°; literature (10) gave m.p. 214° for the product obtained on reduction of 6-nitro-12-chlorochrysene. Oxidation of the amine with sodium dichromate as for the bromo compound gave *12-chloro-5,6-chrysenequinone*, crystallizing from acetic acid in shiny red needles, m.p. 249°; lit (10) m.p. 248°. Violet coloration with sulfuric acid.

Condensation of 6-aminochrysene with aromatic aldehydes. A solution of 6-aminochrysene (1 mole) and the aldehyde (1 mole) in the minimum amount of ethanol was refluxed for 12 hours; the Schiff base which precipitated on cooling in almost theoretical yield was recrys-

tallized from ethanol; its color deepened in proportion to the number of rings possessed by the aldehyde.

6-(p-Chlorobenzal)aminochrysene was pale yellow needles, m.p. 183°.

Anal. Calc'd for $C_{25}H_{16}ClN$: C, 82.1; H, 4.4.
Found: C, 82.0; H, 4.5.

6-(p-Anisal)aminochrysene was bright yellow prisms, m.p. 155°.

Anal. Calc'd for $C_{26}H_{19}NO$: C, 86.4; H, 5.3.
Found: C, 86.1; H, 5.4.

6-(5-Acenaphthylidene)aminochrysene was dark yellow prisms, m.p. 206°.

Anal. Calc'd for $C_{31}H_{21}N$: C, 91.4; H, 5.2.
Found: C, 91.2; H, 5.1.

6-(3-Pyrenylidene)aminochrysene was shiny red needles, m.p. 245°.

Anal. Calc'd for $C_{35}H_{21}N$: C, 92.3; H, 4.6.
Found: C, 92.2; H, 4.5.

6-(2,5-Dimethyl-1-pyrryl)chrysene (VII). A mixture of 1 g. of 6-aminochrysene and 2 g. of acetonylacetone was refluxed until the clear solution had turned into a crystalline mass; ethanol was added, and the solid obtained was recrystallized from acetic acid, giving in almost quantitative yield yellowish needles, m.p. 253°.

Anal. Calc'd for $C_{24}H_{19}N$: C, 89.7; H, 5.9.
Found: C, 89.7; H, 6.0.

6-(2-Methyl-5-n-butyl-1-pyrryl)chrysene (VIII) crystallized from ethanol in almost colorless needles, m.p. 184°.

Anal. Calc'd for $C_{27}H_{25}N$: C, 89.3; H, 6.9.
Found: C, 89.1; H, 7.1.

SUMMARY

1. The chemistry of 6-aminochrysene has been investigated, and several of its derivatives have been prepared for biological examination for potential leukopenia-producing activity.

2. The constitution of the halogenation products of 6-acetylaminochrysenes has been determined.

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