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

SOME REACTIONS OF 6-AMINOCHRYSENE

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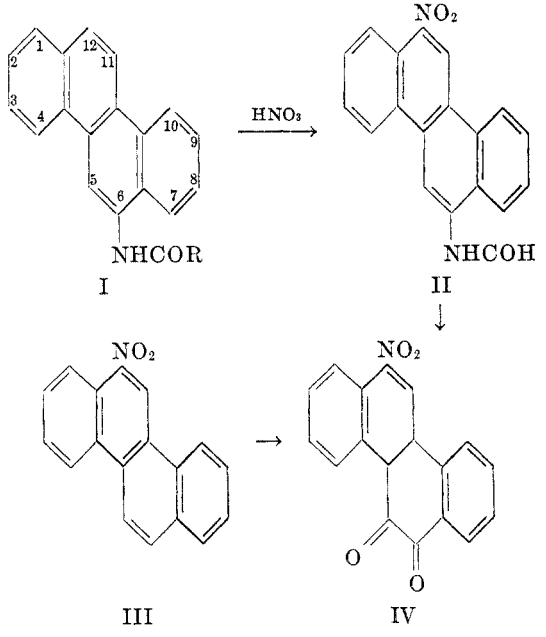
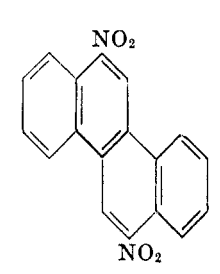
In view of the interesting biological properties of 6-aminochrysene as an inhibitor of adenocarcinoma of the breast in mice, and as a leukopenia-provoking agent (1), the chemistry of this molecule was thought worthy of a more thorough investigation.

It was recently found (2) that 6-acylaminochrysenes (I) undergo chlorination and bromination at the 12-position, and that the halogenation products thus obtained undergo chromic acid oxidation at the 5,6-bond, to give 12-chloro- and 12-bromo-5,6-chrysenequinone. In the present work, the nitration of the 6-acylaminochrysenes is considered, and this reaction, performed in acetic acid at room temperature, was found to give 12-nitro-6-acylaminochrysenes (II) exclusively. Because of the poor solubility in acetic acid of the 6-acylaminochrysenes derived from the lower fatty acids, 6-*n*-valerylaminochrysene and higher homologs were preferred for this nitration. The site of substitution was determined by oxidation with sodium dichromate in acetic acid, which eliminated the acylamino group to give a red nitrochrysenequinone melting at 303°; this compound must have been 12-nitro-5,6-chrysenequinone (IV), since it could also be readily prepared by a similar oxidation of 6-nitrochrysene (III). When condensed with *o*-phenylenediamine, both samples of this quinone afforded the same phenazine, which confirmed their identity.



Some confusion exists in the literature concerning 12-nitro-5,6-chrysenequinone. In 1891, Abegg (3) described a nitro-5,6-chrysenequinone melting at 252°, which he obtained by treating 6-acetylaminochrysene with dilute nitric acid, and claimed its identity with the quinone which Bamberger and Burgdorf (4) had prepared by the chromic acid oxidation of 6-nitrochrysene and for which they gave no melting point. If this were so, Abegg's substance would then be 12-nitro-5,6-chrysenequinone. The present work shows this not to be the case, and that Abegg's quinone was either 12-nitro-5,6-chrysenequinone in a very impure state, or one of its isomers, possibly the x-nitro-5,6-chrysenequinone melting at 256° which Singh and Dutt (5) obtained in the nitration of 5,6-chrysenequinone with heating.



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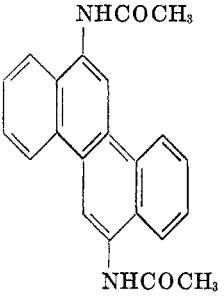

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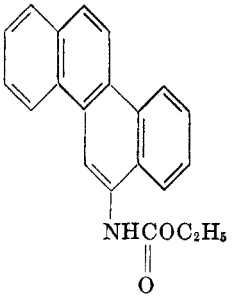

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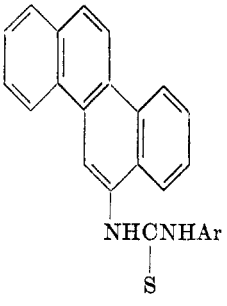

VIII

The determination of the site of nitration in 6-acylaminochrysenes provides a proof of constitution for the dinitration-product of chrysene (6), which had rightly been assumed to be 6,12-dinitrochrysene (V), though no direct proof had been offered. 12-Nitro-6-acetylaminochrysene gave, on reductive acetylation, 6,12-*bis*(acetylamino)chrysene (VI), identical with the acetylation-product of the diamine (7) prepared from V.

In view of the activity of urethan in leukemia (8), 6-chrysylurethan (VII) was prepared from 6-aminochrysene and ethyl chloroformate in pyridine, and found to show leukopenia-inducing properties; for similar biological testing, several N-aryl-N′-(6-chrysenyl)thioureas (VIII) were prepared from the same amine and various aryl isothiocyanates.

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EXPERIMENTAL

12-Nitro-6-n-valerylaminochrysene (II; R = n-C_4H_9). A solution of 2 g. of 6-n-valerylaminochrysene (2) in 125 ml. of acetic acid was treated at 35° with 0.5 g. of fuming nitric acid (*d.* 1.49), and the mixture was kept for one hour at room temperature; the solid precipitate obtained was collected, washed with acetic acid and water, and recrystallized from acetic acid as shiny, yellow, sublimable needles, m.p. 298–299°. Yield, 2 g.

Anal. Calc'd for $C_{23}H_{20}N_2O_3$: C, 74.2; H, 5.4.
Found: C, 73.9; H, 5.4.

12-Nitro-6-caproylaminochrysene (II; R = n-C_5H_{11}) was prepared in a similar yield from 2 g. of 6-caproylaminochrysene and 0.5 g. of nitric acid in 110 ml. of acetic acid; it crystallized from acetic acid in shiny, yellow, sublimable needles, m.p. 274°.

Anal. Calc'd for $C_{24}H_{22}N_2O_3$: C, 74.6; H, 5.7.
Found: C, 74.3; H, 5.9.

12-Nitro-6-lauroylaminochrysene (II; R = n-$C_{11}H_{23}$) was prepared from 1.5 g. of 6-lauroylaminochrysene and 0.4 g. of nitric acid in 80 ml. of acetic acid. Yield, 1.4 g. of a product crystallizing from acetic acid in silky yellow needles, m.p. 232–233°.

Anal. Calc'd for $C_{30}H_{34}N_2O_3$: C, 76.6; H, 7.2.
Found: C, 76.8; H, 7.3.

12-Nitro-5,6-chrysenequinone (IV). (a) A mixture of 2.5 g. of 6-nitrochrysene (9), 15 g. of sodium dichromate, and 200 ml. of acetic acid was refluxed for 12 hours; the solid obtained on cooling was collected, washed with water, and recrystallized twice from acetic acid. Yield, 1.2 g. of silky, bright red, sublimable needles, m.p. 302–303°.

Anal. Calc'd for $C_{18}H_9NO_4$: C, 71.3; H, 3.0; N, 4.6.
Found: C, 70.8; H, 2.9; N, 4.3.

(*b*) A mixture of 1 g. of 12-nitro-6-n-valerylaminochrysene, 5 g. of sodium dichromate, and 125 ml. of acetic acid was refluxed for six hours; the precipitate obtained on cooling was washed with water and recrystallized from acetic acid. Yield, 0.6 g. of a product identical with the above.

The *quinoxaline* obtained with o-phenylenediamine in acetic acid crystallized from pyridine in silky yellow needles, m.p. 280–281°, and gave a violet coloration with sulfuric acid. Newman and Cathcart (9) oxidized 6-nitrochrysene to a product which was not purified, but which yielded with o-phenylenediamine a quinoxaline of m.p. 277.6–279.6°. The *methylquinoxaline* obtained with 4-methyl-1,2-diaminobenzene crystallized from pyridine in silky, yellow, sublimable needles, m.p. 309–310°; violet coloration with sulfuric acid.

Anal. Calc'd for $C_{25}H_{15}N_3O_2$: N, 10.8. Found: N, 10.6.

The *heptacyclic quinoxaline* obtained on condensation with 2,3-diaminonaphthalene in pyridine crystallized from the latter solvent in silky orange needles, m.p. 348–350°; it gave a deep violet coloration with sulfuric acid.

Anal. Calc'd for $C_{28}H_{15}N_3O_2$: N, 9.9. Found: N, 9.6.

Conversion of 6-acetylaminochrysene to 6,12-bis(acetylamino)chrysene (VI). A cooled solution of 1 g. of 6-acetylaminochrysene in 100 ml. of acetic acid was treated in the usual way with 0.4 g. of fuming nitric acid, and the mixture was kept overnight at room temperature. The crude 12-nitro-6-acetylaminochrysene obtained on dilution with water was reduced with an excess of stannous chloride in boiling ethanol. The precipitate obtained was dried, and was treated with acetyl chloride in pyridine in the usual way, to give *6,12-bis(acetylamino)chrysene*, which crystallized from acetic acid in fine colorless prisms, m.p. 364–365°; acetylation of the diamine prepared from 6,12-dinitrochrysene according to the literature (7) yielded the same compound.

6-Chrysenylurethan (VII). To a well-cooled solution of 2.5 g. of 6-aminochrysene in 50 ml. of dry pyridine, 1.2 g. of ethyl chloroformate was added dropwise with stirring; the mixture was kept at room temperature for five minutes, and treated with dilute hydrochloric acid. Yield, 98% of a product crystallizing from benzene in silky colorless needles, m.p. 222–223°. Abegg (10) reported m.p. 214° for 6-chrysylurethan prepared from the amine and ethyl chloroformate in an aqueous solution of sodium hydroxide.

Anal. Calc'd for $C_{21}H_{17}NO_2$: C, 80.0; H, 5.4.
Found: C, 80.2; H, 5.5.

N-β-Naphthyl-N'-(6-chrysenyl)thiourea. A solution of 2.5 g. of 6-aminochrysene and 1.8 g. of β-naphthyl isothiocyanate in ethanol was gently refluxed for 15 minutes; the precipitate which was obtained in a quantitative yield on cooling, crystallized from benzene in fine yellowish needles, m.p. 248–250°; the substance slowly decomposed on progressive heating above 200°, with the formation of β-naphthyl isothiocyanate.

Anal. Calc'd for $C_{29}H_{20}N_2S$: N, 6.5. Found: N, 6.4.

N-p-Phenetyl-N'-(6-chrysenyl)thiourea was prepared similarly from *p*-ethoxyphenyl isothiocyanate. It crystallized from benzene in fine yellowish needles, m.p. 188–189° (decomp.).

Anal. Calc'd for $C_{27}H_{22}N_2OS$: N, 6.6. Found: N, 6.4.

N-p-Bromophenyl-N'-(6-chrysenyl)thiourea was prepared from *p*-bromophenyl isothiocyanate. It crystallized from ethanol in yellowish prisms, m.p. 218–219°, with decomposition to *p*-bromophenyl isothiocyanate.

Anal. Calc'd for $C_{25}H_{17}BrN_2S$: N, 6.1; S, 7.0.
Found: N, 6.0; S, 7.2.

SUMMARY

1. The nitration of 6-acylaminochrysenes has been investigated, and is shown to occur at the 12-position.

2. A number of derivatives of 6-aminochrysene have been prepared for biological examination as potential anti-leukemia agents.

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