[CONTRIBUTION NO. 129 FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF TENNESSEE]

NITROGEN ISOLOGS OF CHRYSENE[1]

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Received October 7, 1953

In order to extend our knowledge of the influence of chemical constitution upon cytological activity, several nitrogen isologs of chrysene have been prepared. It is now generally agreed that chrysene possesses little, if any, cancerigenic powers (1, 2). On the other hand, it has been observed that chrysene inhibits the growth rate of Jensen and Walker tumors (3). Thus, it will be of interest to ascertain whether inclusion of nitrogen in the chrysene nucleus will enhance the stimulatory or inhibitory powers of chrysene.

Naphth[2,1-*f*]isoquinoline (2-azachrysene, V) was prepared by the following sequence of operations. 1-Phenanthrenecarboxaldehyde (4) formed a cyanohydrin with difficulty and was therefore converted instead to 1-(β-nitrovinyl)-phenanthrene (I) in 85% yield by the action of alkaline nitromethane. Lithium aluminum hydride reduction of the nitrovinyl compound afforded a quantitative yield of β-(1-phenanthryl)ethylamine (II). An attempt to cyclize the amine directly by the Pictet-Spengler reaction (5) was unsuccessful. Heating the amine with formic acid at 150–160° yielded β-(1-phenanthryl)ethylformamide (III). Of numerous modifications of the Bischler-Napieralski reaction (6) tried, cyclization could be effected only by the action of phosphorus oxychloride and stannic chloride on the amide in refluxing nitrobenzene (7), proceeding in 29% yield. The 3,4-dihydronaphth[2,1-*f*]isoquinoline (IV) obtained in this way was dehydrogenated with palladium-charcoal (8) yielding 34% of the desired naphth-[2,1-*f*]isoquinoline (V). The over-all yield from phenanthrene was 0.2%.

The synthesis of benzo[c]phenanthridine (5-azachrysene, VII) required 2-phenylnaphthalene as an intermediate. The latter was prepared by the Gomberg reaction (9) in 7% yield. Nitration of 2-phenylnaphthalene and reduction of the nitro compound afforded 2-phenyl-1-naphthylamine (10). 1-Formamido-2-phenylnaphthalene (VI) was prepared and cyclized to benzo[c]phenanthridine (VII) by the method previously discussed (7). Although this compound has been prepared previously (11), the method described herein is superior in point of convenience and yield.

A compound believed to be quinolino[6,5-*f*]quinoline (1,7-diazachrysene, IX) was prepared from 6-nitro-2-naphthylamine (12) by two separate routes. The nitroamine was reduced catalytically to 2,6-naphthalenediamine (VIII) (13) in 74% yield. Subjection of the diamine to a double Skraup reaction (14) transformed it into quinolino[6,5-*f*]quinoline in 20% yield. 8-Nitrobenzo[*f*]quinoline (X), a known compound, was prepared by a Skraup reaction (15) with 6-nitro-

[1] The authors are grateful for the financial support of the National Cancer Institute of the National Institutes of Health.

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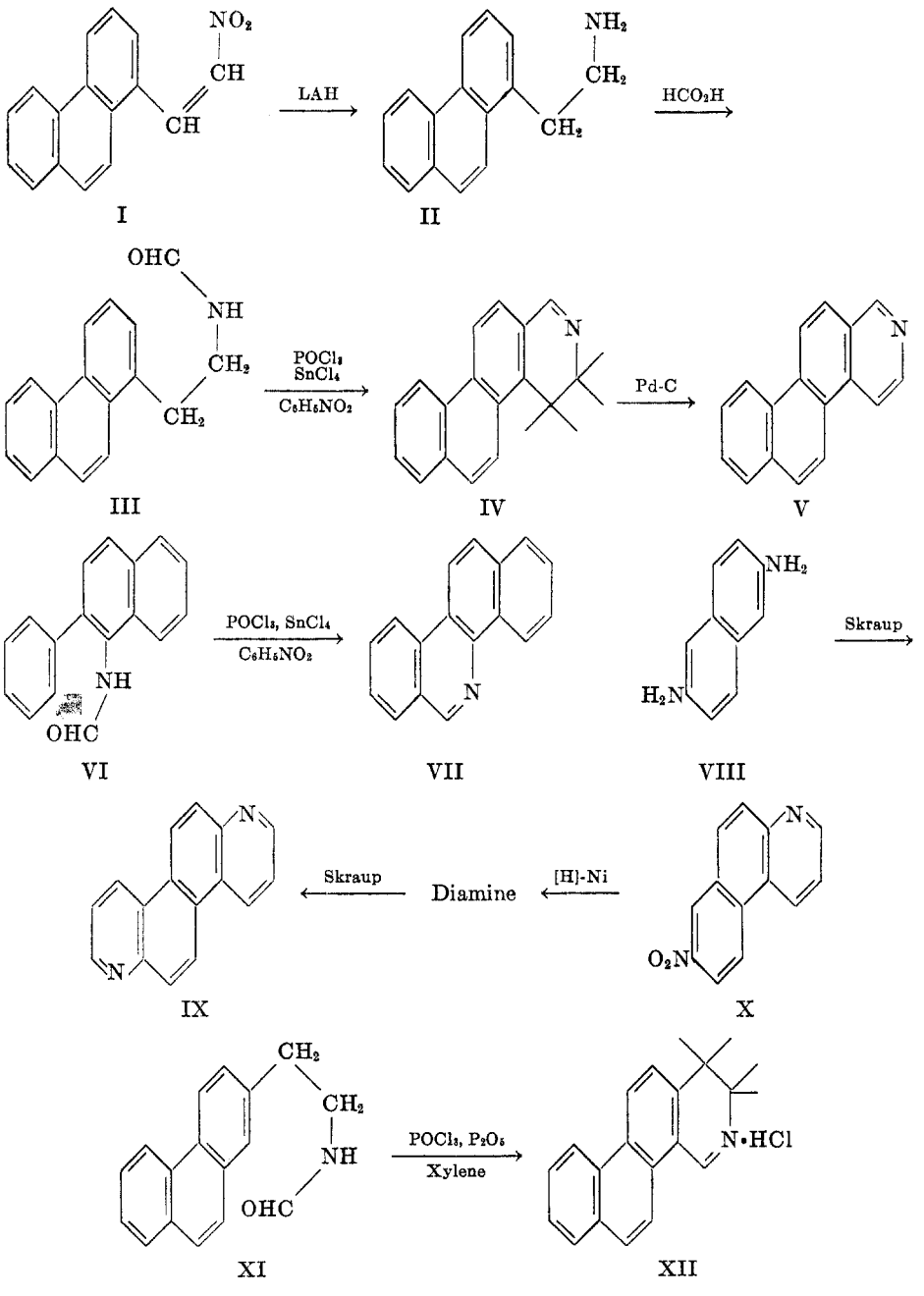

2-naphthylamine. By means of reduction and a second Skraup reaction, quinolino[6,5-*f*]quinoline was again produced, thus proving the point of attachment of at least one nitrogen ring of the final product.[4]

[4] The structure of quinolino[6,5-*f*]quinoline was not proved because 2-naphthylamines

β-(2-Phenanthryl)ethylformamide (XI) was prepared from the known β-(2-phenanthryl)ethylamine (16) and cyclized under Bischler-Napieralski conditions, yielding a small quantity of a product whose composition corresponded fairly well to that of the desired 1,2-dihydronaphth[1,2-*h*]isoquinoline hydrochloride (XII). However, if cyclization occurred at the 3-position of the phenanthrene nucleus, the product would be 3,4-dihydronaphth[2,1-*g*]isoquinoline hydrochloride, and this possibility has not been excluded. A Pictet-Spengler reaction with β-(2-phenanthryl)ethylamine and formaldehyde yielded an impure hydrochloride, m.p. 247–251°, which could not be further purified. There was insufficient material for further study.

EXPERIMENTAL[5]

1-(β-Nitrovinyl)phenanthrene (I). To a solution of 5 g. (0.025 mole) of 1-phenanthrenecarboxaldehyde (4) dissolved in 100 ml. of absolute ethanol was added 3.2 g. (0.05 mole) of nitromethane and the solution was cooled to 0°. An ice-cold solution of 2.5 g. (0.04 mole) of potassium hydroxide in 50 ml. of absolute ethanol was added dropwise with stirring over a period of 20 minutes, a white solid separating. The solid was dissolved by adding ice-water and the whole was poured into 100 ml. of ice-cold 10% hydrochloric acid. The yellow solid which separated was collected, washed with water, and dried. Recrystallization from benzene afforded 85% of bright-yellow needles, m.p. 165–167°.

Anal. Calc'd for $C_{16}H_{11}NO_2$: C, 77.09; H, 4.45; N, 5.62.
Found: C, 77.27; H, 4.60; N, 5.46.

β-(1-Phenanthryl)ethylamine (II). 1-(β-Nitrovinyl)phenanthrene (5.3 g., 0.022 mole) was placed in a Soxhlet extractor and extracted with ether into a stirred ethereal solution (300 ml.) containing 4 g. (0.11 mole) of dissolved lithium aluminum hydride. After all the solid had been extracted into the hydride solution, the reaction mixture was allowed to stir and reflux for an additional one-half hour and then the complex and excess hydride were decomposed by water. The ethereal solution was filtered, dried, and treated with dry hydrogen chloride. The precipitated hydrochloride crystallized from absolute ethanol as shiny white needles, m.p. 278–280° dec. The yield was quantitative.

Anal. Calc'd for $C_{16}H_{16}ClN$: C, 74.55; H, 6.26; N, 5.44.
Found: C, 74.56; H, 6.13; N, 5.38.

β-(1-Phenanthryl)ethylformamide (III). The formylation was accomplished by heating the amine with 1.5 equivalents of anhydrous formic acid at 150–160° for 30 minutes. Sublimation of the residue at 140–150° (bath)/0.5 μ yielded a solid, m.p. 93–96°.

Anal. Calc'd for $C_{17}H_{15}NO$: C, 81.90; H, 6.06; N, 5.62.
Found: C, 82.06; H, 6.18; N, 5.44.

3,4-Dihydronaphth[2,1-f]isoquinoline (IV). A mixture of 4.5 g. (0.018 mole) of β-(1-phenanthryl)ethylformamide, 36 g. (0.23 mole) of phosphorus oxychloride, 2.31 g. (0.009 mole) of stannic chloride, and 57 ml. of nitrobenzene was refluxed for four hours. The cooled mixture was carefully treated with 100 ml. of water and was steam-distilled to remove the nitrobenzene. The cooled residue was made basic by the addition of solid sodium hydroxide. The flocculent precipitate was collected, dried, decolorized, and recrystallized from ethyl acetate. The shiny, light-tan leaflets (1.2 g., 29%) melted at 214–216°.

Anal. Calc'd for $C_{17}H_{13}N$: C, 88.28; H, 5.66; N, 6.06.
Found: C, 88.07; H, 5.64; N, 6.06.

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invariably close to the 1-position, sometimes ejecting another substituent to do so, and 2-aminophenanthrene also cyclizes only to the 1-position [Manske and Kulka, *Org. Reactions*, **7**, 59 (1953)].

[5] Microanalyses by Galbraith Laboratories, Knoxville, Tenn. Melting points were obtained on a calibrated apparatus.

A solution of the free base in benzene was treated with ethanolic picric acid and the *picrate* which formed was collected, washed with hot ethanol, and dried. It melted at 243–246° dec.

Anal. Calc'd for $C_{23}H_{16}N_4O_7$: C, 60.00; H, 3.50; N, 12.17.
Found: C, 59.55; H, 3.60; N, 11.82.

Naphth[2,1-f]isoquinoline (V). A solution of 1.2 g. (0.0052 mole) of 3,4-dihydronaphth[2,1-*f*]isoquinoline in 10 ml. of α-methylnaphthalene was refluxed with 300 mg. of 20% palladium-charcoal for six hours in a stream of carbon dioxide, the hydrogen being collected in an azotometer. The reaction mixture was diluted with 100 ml. of cyclohexane, heated to boiling, and filtered. The filtrate was treated with dry hydrogen chloride, filtered, and the collected solid was washed thoroughly with cyclohexane. The dried solid was suspended in water, made basic by the addition of solid sodium hydroxide, filtered, and the residue was washed with water, and dried. After decolorization and recrystallization from ethyl acetate, there was obtained 0.4 g. (34%) of light-tan crystals, m.p. 224–226°.

Anal. Calc'd for $C_{17}H_{11}N$: C, 89.05; H, 4.84; N, 6.11.
Found: C, 88.84; H, 4.96; N, 6.13.

1-Formamido-2-phenylnaphthalene (VI). A mixture of 2.04 g. (0.0093 mole) of 2-phenyl-1-naphthylamine (10) and 1.5 equivalents of anhydrous formic acid was heated at 150–160° for 30 minutes. After recrystallization from benzene and ligroin, the amide melted at 170–176°.

Anal. Calc'd for $C_{17}H_{13}NO$: C, 82.57; H, 5.30; N, 5.67.
Found: C, 82.76; H, 5.58; N, 5.49.

Benzo[c]phenanthridine (VII). A mixture of 2 g. (0.0081 mole) of 1-formamido-2-phenylnaphthalene, 16 g. (0.104 mole) of phosphorus oxychloride, 1.03 g. (0.004 mole) of stannic chloride, and 19 ml. of nitrobenzene was refluxed for four hours. When the reaction mixture had cooled 10 ml. of water was carefully added and the mixture was steam-distilled. The cooled residue was made basic and the solid which separated was sublimed at 150–170° (bath)/5–10 μ. The sublimate was decolorized and recrystallized from ethanol to yield 1.0 g. (60%) of yellow crystals melting at 133.5–135°. The picrate melted at 256–257° dec. Ritchie (11) reported a melting point of 135° for the free base and 255–256° for the picrate.

8-Aminobenzo[f]quinoline. A mixture of 4.6 g. (0.0205 mole) of 8-nitrobenzo[*f*]quinoline (15), prepared in 55% yield from 6-nitro-2-naphthylamine (12), 150 ml. of absolute ethanol, and 3 ml. of triethylamine was shaken with Raney nickel and hydrogen at room temperature and 3 atmospheres of pressure for six hours. The catalyst was removed from the hot solution by filtration and 3.7 g. (93%) of the product was obtained from the ethanol, and melted at 219–223°.

Quinolino[6,5-f]quinoline (IX). *Procedure A.* To a mixture of 3.7 g. (0.019 mole) of 8-aminobenzo[*f*]quinoline, 15 g. (0.163 mole) of glycerol, and 6 g. (0.042 mole) of arsenic acid was added 15 g. of concentrated sulfuric acid, slowly with cooling and stirring. The reaction mixture was heated for ten minutes at 150° after which vigorous foaming necessitated termination of the reaction. The mixture was poured into 300 ml. of water, heated to 90°, and filtered. The filtrate was cooled and made basic by the addition of solid sodium hydroxide. The entire mixture was extracted continuously for 40 hours with carbon tetrachloride. Removal of the carbon tetrachloride by distillation afforded a light-tan solid which upon decolorization and recrystallization from absolute ethanol was obtained as 0.90 g. (20%) of light-tan, lustrous plates, m.p. 284.5–285.5°.

Procedure B. To an intimate mixture of 2.9 g. (0.018 mole) of 2,6-naphthalenediamine (13), 13 g. (0.14 mole) of glycerol, and 5 g. (0.035 mole) of arsenic acid, was added slowly with stirring and cooling, 13 g. of concentrated sulfuric acid. When the mixture was heated to 150° a vigorous reaction ensued, following which the contents of the flask was refluxed for 30 minutes. The mixture was then poured into 200 ml. of water and the product was isolated as described in *Procedure A.* There was obtained 0.85 g. (20%) of crystalline product, m.p. 283.5–285°, either alone or in admixture with the product obtained in *Procedure A.*

Anal. Calc'd for $C_{16}H_{10}N_2$: C, 83.45; H, 4.38; N, 12.17.

Found: C, 83.22; H, 4.54; N, 12.40.

The *dihydrochloride* was prepared by treating an ethereal solution of the free base with anhydrous HCl. It was recrystallized from a mixture of ethanol and 2-propanol, appearing as short brown needles, m.p. 284–285°, and very soluble in water.

Anal. Calc'd for $C_{16}H_{12}Cl_2N_2$: N, 9.24. Found: N, 9.16.

β-(2-Phenanthryl)ethylformamide (XI). This amide was prepared in the usual manner and after recrystallization from benzene and petroleum ether, the fluffy white solid melted at 121–122°.

Anal. Calc'd for $C_{17}H_{15}NO$: C, 81.90; H, 6.06; N, 5.62.
Found: C, 82.09; H, 5.92; N, 5.54.

1,2-Dihydronapth[1,2-h]isoquinoline hydrochloride (XII). Two grams (0.008 mole) of β-(2-phenanthryl)ethylformamide was dissolved in 50 ml. of dry xylene, treated with 19.7 g. (0.130 mole) of phosphorus oxychloride and 10.3 g. (0.08 mole) of phosphorus pentoxide, and refluxed for two hours with stirring. The mixture was poured over 50 g. of ice and the aqueous layer was made basic with sodium hydroxide. The flocculent precipitate was extracted with benzene, dried, decolorized, and treated with hydrogen chloride. The yellow hydrochloride melted at 197–200° dec. after recrystallization from absolute ethanol and ether.

Anal. Calc'd for $C_{17}H_{14}ClN \cdot H_2O$: C, 71.44; H, 5.64; N, 4.90; Cl, 12.41.
Found: C, 72.51; H, 5.57; N, 4.71; Cl, 12.59.

SUMMARY

Naphth[2,1-*f*]isoquinoline and quinolino[6,5-*f*]quinoline have been prepared for the first time. An improved synthesis for benzo[*c*]phenanthridine is described. 1,2-Dihydronaphth[1,2-*h*]isoquinoline hydrochloride was prepared by a reaction which was not unambiguous.

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REFERENCES

(1) SHEAR AND LEITER, *J. Natl. Cancer Inst.*, **2**, 241 (1941).
(2) COULSON, *Advances in Cancer Research*, Vol. I, Academic Press, Inc., New York, N. Y., 1953, p. 1.
(3) HADDOW AND ROBINSON, *Proc. Roy. Soc.* (*London*), **B122**, 442 (1937).
(4) BACHMANN, *J. Am. Chem. Soc.*, **57**, 555 (1935); BACHMANN AND BOATMAN, *J. Am. Chem. Soc.*, **58**, 2097 (1936).
(5) WHALEY AND GOVINDACHARI, *Org. Reactions*, **6**, 151 (1951).
(6) WHALEY AND GOVINDACHARI, *Org. Reactions*, **6**, 74 (1951).
(7) OCKENDEN AND SCHOFIELD, *J. Chem. Soc.*, 717 (1953).
(8) LINSTEAD AND THOMAS, *J. Chem. Soc.*, 1130 (1940).
(9) ELKS, HAWORTH, AND HEY, *J. Chem. Soc.*, 1284 (1940); HAWORTH AND HEY, *J. Chem. Soc.*, 366, 378 (1940).
(10) HEY AND LAWTON, *J. Chem. Soc.*, 374 (1940).
(11) RITCHIE, *J. Proc. Roy. Soc. N. S. Wales*, **78**, 173 (1944).
(12) SAUNDERS AND HAMILTON, *J. Am. Chem. Soc.*, **54**, 638 (1932).
(13) HAZLET AND DORNFELD, *J. Am. Chem. Soc.*, **66**, 1781 (1944); SWEET AND HAMILTON, *J. Am. Chem. Soc.*, **56**, 2408 (1934).
(14) FINGER AND SPITZ, *J. prakt. Chem.*, [2], **79**, 445 (1909).
(15) CLEM AND HAMILTON, *J. Am. Chem. Soc.*, **62**, 2349 (1940).
(16) MOSETTIG AND MAY, *J. Am. Chem. Soc.*, **60**, 2962 (1938).