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NITROGEN ISOLOGS OF BENZO[*a*]PYRENE[1]

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Benzo[*a*]pyrene is one of the most powerful carcinogens known and is considered to be responsible for the cancerigenic properties of coal tar (1). A number of synthetic derivatives of this compound have been prepared and evaluated (2) but few nitrogen isologs have been prepared and examined for carcinogenicity or anticarcinogenicity (3). The present study was undertaken to provide additional information regarding the correlation between structure and activity of isosteric compounds and is an extension of the work reported on chrysene isologs (4). This line of research is still largely unexplored and significant correlations will be contingent upon the availability of a greater percentage of the theoretically possible isologs. For instance, no compounds are known which have nitrogen atoms in the 1, 2, or 3 positions[3] of benzo[*a*]pyrene, which are known to be involved in metabolism of the parent hydrocarbon. Also, nitrogen atoms have not yet been substituted in the K-regions, and syntheses along these lines have been projected.

The known (5) pyreno[1, 2-*b*]pyridine (pyrenoline, I) was prepared in 33% yield by a Skraup reaction with 1-aminopyrene.[4] 2-Aminopyrene was synthesized by the somewhat devious route of Vollmann (5) and converted to pyreno[2, 1-*b*]-pyridine (II) in 22% yield by the Skraup reaction.

Pyrene-1-carboxaldehyde (5) was selected as a starting material in the preparation of pyreno[2,1-*c*]pyridine. The aldehyde did not form a cyanohydrin satisfactorily but was converted in 36% yield to 1-(β-nitrovinyl)pyrene (III), m.p. 174–177°, by the method of Bograchov (6). By an alternate method of preparing nitrostyrenes (7), a 94% yield of the geometrical isomer (probably *trans*), m.p. 195.5–196°, was obtained. Reduction of the nitrovinyl compounds with lithium aluminum hydride afforded a quantitative yield of 1-(β-aminoethyl)pyrene hydrochloride (IV). An attempt to cyclize the amine with formaldehyde by the Pictet-Spengler reaction (8) yielded a hydrochloride, m.p. 281–288° dec., which could not be purified sufficiently for corroborative analysis. The amine was converted to 1-(β-formamidoethyl)pyrene (V) by heating it with formic acid. Numerous attempts were made to cyclize the formyl derivative by the Bischler-Napieralski reaction (9), but the most efficient conditions involved the use of phosphorus pentoxide in refluxing *p*-cymene, which yielded 9,10-dihydropyreno[2,1-*c*]-

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[3] This system of numbering is in accordance with Patterson and Capell, "The Ring Index", Reinhold Publishing Co., New York, 1940, R. I. 3317.

[4] This numbering of substituted pyrenes follows that of recent issues of *Chem. Abstracts* indexes.

pyridine (VI) in 25% yield. This substance was dehydrogenated in 56% yield by means of palladium-charcoal (10) to pyreno[2,1-*c*]pyridine (VII).

Various attempts to prepare pyreno[1,2-*c*]pyridine by the Pomeranz-Fritsch reaction (11) with pyrene-1-carboxaldehyde and aminoacetal were unsuccessful.

Also unsuccessful were various attempts to cyclize the diformyl derivative of 2-(2-aminophenyl)-1-naphthylamine to benzo[*j*]pyrido[2,3,4,5-*lmn*]phenanthridine (IX). The diformyl derivative was prepared through several steps from 1-nitro-2-(2-nitrophenyl)naphthalene (VIII), which was formed by an Ullmann reaction of 1-nitro-2-bromonaphthalene with *o*-nitrobromobenzene. The dinitro compound was reduced to 2-(2-aminophenyl)-1-naphthylamine, which was converted to the diformyl derivative by heating with formic acid.

Incidental to these studies the thiosemicarbazone of pyrene-1-carboxaldehyde was prepared in 81% yield by the usual method.

EXPERIMENTAL[5]

Pyreno[2,1-b]pyridine (II). To a mixture of 10 g. (0.039 mole) of 2-aminopyrene hydrochloride (5), 28 g. (0.3 mole) of glycerol, and 11 g. (0.08 mole) of arsenic acid was added 28 g. of concentrated sulfuric acid slowly and with stirring. The mixture was heated to 145° whereupon a vigorous reaction ensued, accompanied by evolution of hydrogen chloride. After 45 minutes of heating, the mixture was poured into 600 ml. of water, and made basic by the addition of ammonia. The precipitate was collected, dried, and extracted with cyclohexane. Removal of the cyclohexane and decolorization and recrystallization of the residue from ethyl acetate afforded 2.2 g. (22%) of rust-colored needles, m.p. 188.5–191°.

Anal. Calc'd for $C_{19}H_{11}N$: C, 90.09; H, 4.38; N, 5.53.
Found: C, 89.62; H, 4.54; N, 5.77.

1-(β-Nitrovinyl)pyrene (III). A mixture of 25 g. (0.11 mole) of pyrene-1-carboxaldehyde (5), 15 g. of ammonium acetate, 45 g. (0.75 mole) of nitromethane, and 400 ml. of glacial acetic acid was refluxed for two hours. The reaction mixture was poured into 2 l. of ice and water, allowed to stand overnight, and filtered. The dried residue was recrystallized from benzene and there was obtained 28 g. (94%) of orange-red crystals, m.p. 195.5–196°.

Anal. Calc'd for $C_{18}H_{11}NO_2$: C, 79.11; H, 4.06; N, 5.13.
Found: C, 79.05; H, 4.12; N, 5.13.

1-(β-Aminoethyl)pyrene hydrochloride (IV). 1-(β-Nitrovinyl)pyrene (18.5 g., 0.068 mole) was extracted over a period of three to six days into a solution of 15 g. (0.4 mole) of lithium aluminum hydride in 1 l. of ether by the Soxhlet extractor technique. One liter of 5% hydrochloric acid was carefully added and the precipitated amine hydrochloride was collected and dried. After recrystallization from ethanol, there was obtained a theoretical yield of product melting at 265–270° dec.

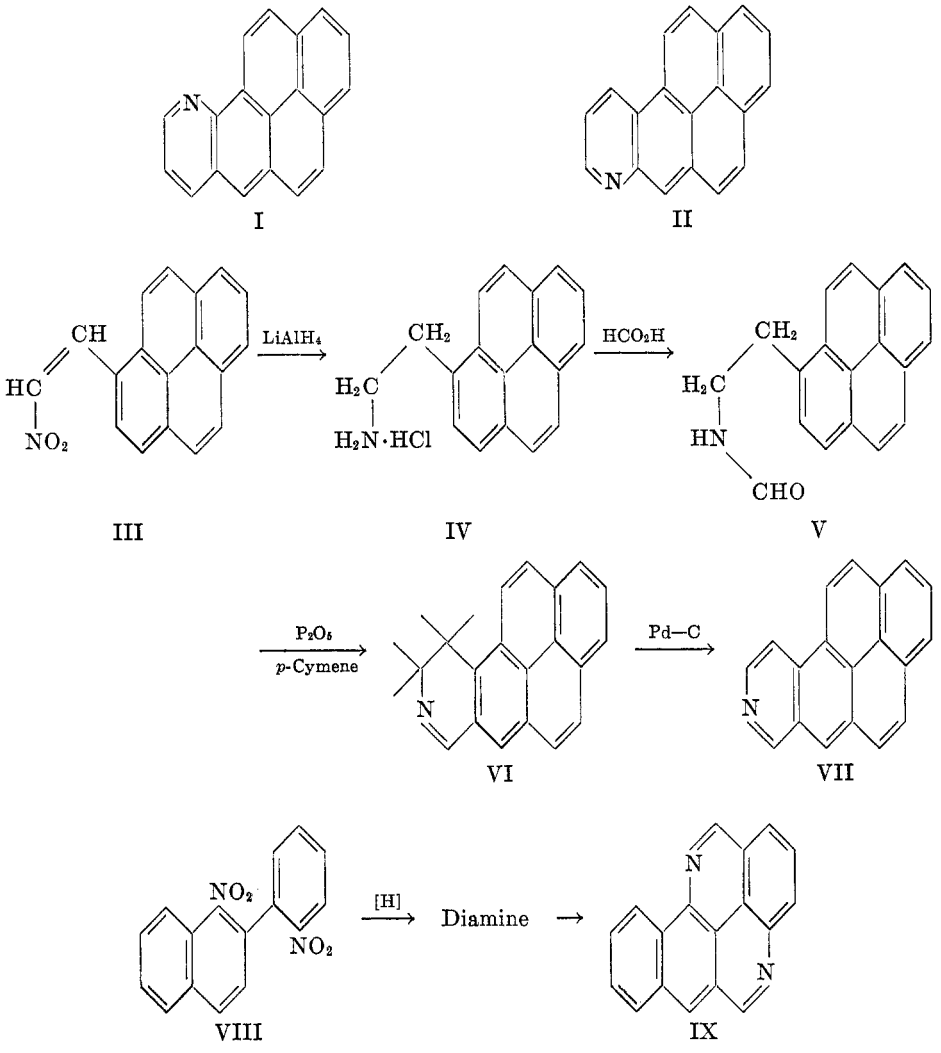
Anal. Calc'd for $C_{18}H_{16}ClN$: C, 76.72; H, 5.72; N, 4.97.
Found: C, 76.53; H, 5.94; N, 5.05.

1-(β-Formamidoethyl)pyrene (V). One gram (0.004 mole) of 1-(β-aminoethyl)pyrene was heated at 150–160° for 30 minutes with 3 ml. of anhydrous formic acid. The brown residual mass was decolorized and recrystallized from benzene after which it melted at 120–122°.

Anal. Calc'd for $C_{19}H_{15}NO$: C, 83.49; H, 5.53; N, 5.13.
Found: C, 83.64; H, 5.51; N, 5.18.

9,10-Dihydropyreno[2,1-c]pyridine (VI). 1-(β-Formamidoethyl)pyrene (38 g., 0.14 mole) was refluxed with a mixture of 85 g. (0.56 mole) of phosphorus pentoxide in 950 ml. of *p*-cymene for one-half hour. After cooling, the *p*-cymene was decanted and the residue was

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



decomposed with 2 l. of ice. The aqueous phase was retained and the residue was leached with a total of 24 l. of boiling 10% hydrochloric acid. The combined acidic solutions were made basic by the addition of solid sodium hydroxide and the flocculent precipitate was collected with the aid of Celite. The residue was dried and extracted with cyclohexane from which the product was obtained as 8.7 g. (25%) of yellow crystals, m.p. 158–161° with slight decomposition.

Anal. Calc'd for $C_{19}H_{13}N$: C, 89.38; H, 5.13; N, 5.49.

Found: C, 88.48, 88.64; H, 4.86, 5.43; N, 5.14, 5.21.

Pyreno[2,1-c]pyridine (VII). A solution of 8.7 g. (0.035 mole) of 9,10-dihydropyreno[2,1-*c*]pyridine in 250 ml. of α-methylnaphthalene was refluxed in a stream of dry nitrogen with 1.8 g. of 20% palladium-charcoal until hydrogen was no longer evolved (six hours). The hot solution was filtered and the catalyst was washed with 100 ml. of hot cyclohexane. The united filtrates were 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 4.8 g. (56%) of tan crystals, m.p. 171–173°. Sublimation at 180–200° (bath)/2–5 μ and recrystallization from ethyl acetate yielded shiny yellow leaflets, m.p. 175.5–176.5°.

Anal. Calc'd for $C_{16}H_{11}N$: C, 90.09; H, 4.38; N, 5.53.
Found: C, 89.89; H, 4.58; N, 5.68.

1-Nitro-2-(2-nitrophenyl)naphthalene (VIII). A mixture of 63 g. (0.25 mole) of 1-nitro-2-bromonaphthalene (12) and 51 g. (0.25 mole) of *o*-nitrobromobenzene was stirred and heated at 225° while 69 g. (1.08 moles) of copper bronze[6] was added over a period of one hour. The mixture was maintained at 230° for 20 minutes, cooled, and leached with boiling ethanol. Concentration of the ethanol yielded a solid which melted at 185–186° after recrystallization from ethyl acetate.

Anal. Calc'd for $C_{16}H_{10}N_2O_4$: C, 65.30; H, 3.43; N, 9.52.
Found: C, 65.53; H, 3.59; N, 9.42.

2-(2-Aminophenyl)-1-naphthylamine. Two grams (0.007 mole) of 1-nitro-2-(2-nitrophenyl)naphthalene was shaken with Raney nickel in a mixture of 150 ml. of absolute ethanol and 5 ml. of triethylamine in a Parr shaker at three atmospheres of hydrogen pressure for 90 minutes. After removal of the catalyst the filtrate was evaporated to dryness and the residue was taken up in ethanol. After decolorization the hot solution was diluted with water and cooled, causing the diamine to crystallize as 1.2 g. (75%) of shiny leaflets, m.p. 118–119.5°.

Anal. Calc'd for $C_{16}H_{14}N_2$: C, 82.02; H, 6.02; N, 11.96.
Found: C, 82.00; H, 6.15; N, 11.87.

The *dihydrochloride* melted at 158–160° after recrystallization from absolute ethanol and ether.

Pyrene-1-carboxaldehyde thiosemicarbazone. A solution of 5 g. (0.0217 mole) of pyrene-1-carboxaldehyde in 75 ml. of boiling ethanol was treated with 5 g. (0.055 mole) of thiosemicarbazide and 7.5 g. (0.061 mole) of sodium acetate. A thick yellow precipitate formed and the reaction mixture was heated to boiling and then allowed to cool. The solid was collected, washed with 50% ethanol and recrystallized from ethyl acetate using a Soxhlet extractor. After a second recrystallization from absolute ethanol the product was obtained as 4.9 g. (81%) of fine yellow needles, m.p. 249–252° dec.

Anal. Calc'd for $C_{18}H_{13}N_3S$: C, 71.26; H, 4.32; N, 13.85.
Found: C, 71.08; H, 4.22; N, 14.01.

SUMMARY

Pyreno[1,2-*b*]pyridine, pyreno[2,1-*b*]pyridine, and pyreno[2,1-*c*]pyridine were prepared for evaluation of their cancerigenic and cancerolytic activities. A number of new intermediates were prepared and characterized. Attempts to synthesize pyreno[1,2-*c*]pyridine and benzo[*j*]pyrido[2,3,4,5-*lmn*]phenanthridine were unsuccessful.

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[6] Copper Lining Bronze XX, U. S. Bronze Powder Works, New York, N. Y.

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