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

POTENTIAL NITROGEN-HETEROCYCLE CARCINOGENS. X. CARBAZOLES WITH ACENAPHTHENE AND CYCLOPENTA[*a*]PHENANTHRENE NUCLEI[1]

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Received October 31, 1950

Acenaphthene has long been recognized as an active mitoclastic agent for plant cells (1), and its skeleton is also to be found in the molecule of potent carcinogenic hydrocarbons such as those of the cholanthrene group. Cyclopenta[*a*]-phenanthrene, the basic hydrocarbon to which are related the essential steroid hormones and sterols, can itself become carcinogenic by adequate substitution with methyl groups (2).

In view of the proved carcinogenicity of many compounds derived from carbazole, it was deemed worth while to synthesize, for biological testing, some substances in whose molecules the carbazole structure is associated with either an acenaphthene or a cyclopenta[*a*]phenanthrene nucleus.

In the acenaphthene series, the intermediate used for the present purpose was 7-keto-7, 8, 9, 10-tetrahydroacephenanthrene (I); this ketone was prepared from acenaphthene and succinic anhydride according to Fieser and Peters' procedure (3), with the modifications that β-(3-acenaphthoyl)propionic acid was reduced by the Wolff-Kishner-Huang-Minlon method (4), and that the cyclization of γ-(3-acenaphthyl)butyric acid was effected with sulfuric acid. The arylhydrazones of ketone I were indolized and the dihydro compounds thus obtained dehydrogenated according to our usual procedure (5), with chloranil.

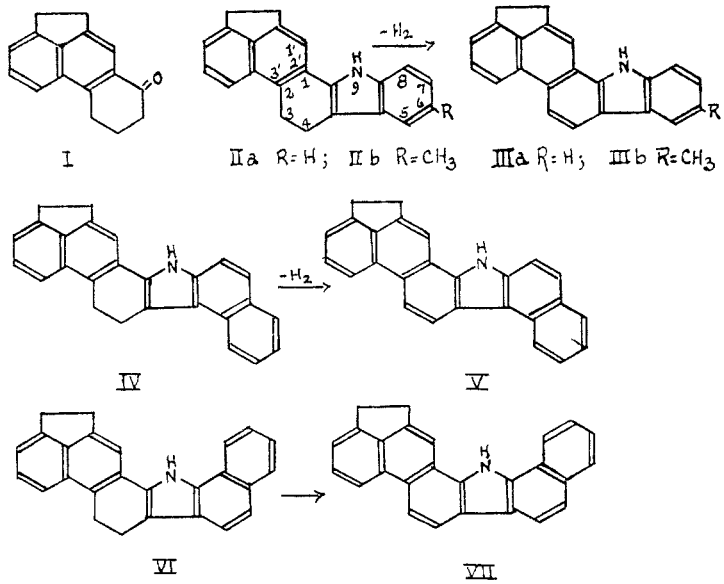
From the phenylhydrazone of ketone I we thus obtained 2′,3′:1,2-acenaphthenocarbazole (IIIa) *via* the 3,4-dihydro compound (IIa); replacement of phenylhydrazine by *p*-tolylhydrazine in this synthesis resulted in 6-methyl-2′,3′:1,2-acenaphthenocarbazole (IIIb), obtained *via* the 3,4-dihydro derivative (IIb).

In the field of heptacyclic compounds, 2′,3′:1,2-acenaphtheno-5,6-benzocarbazole (V) and 2′,3′:1,2-acenaphtheno-7,8-benzocarbazole (VII) were prepared in the same way *via* the 3,4-dihydro derivatives (IV) and (VI), from the β- and α-naphthylhydrazones of ketone I respectively.

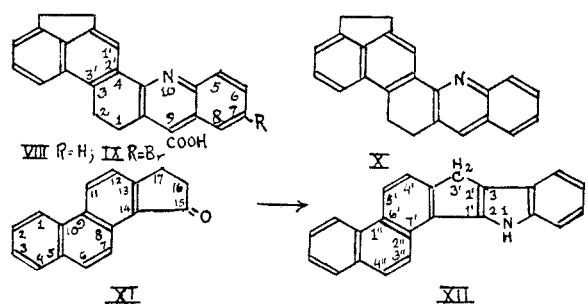
Besides the foregoing carbazole syntheses, ketone I lent itself readily to the preparation of other heterocyclic compounds. Thus, the Pfitzinger-Borsche reaction with isatin yielded 1,2-dihydro-3′,2′:3,4-acenaphthenoacridine-9-carboxylic acid (VIII); with 5-bromoisatin, 7-bromo-1,2-dihydro-3′,2′:3,4-acenaphthenoacridine-9-carboxylic acid (IX) was similarly obtained. These two acids are reminiscent of tetrophan (1,2-dihydro-3,4-benzacridine-9-carboxylic acid), without possessing its potent strychnine-like action. Decarboxylation of acid VIII by pyrolysis gave 1,2-dihydro-3′,2′:3,4-acenaphthenoacridine (X).

[1] Paper IX in this series: Buu-Hoï, Hoán, Khôi, and Xuong, *J. Org. Chem.*, preceding article.

In the cyclopenta[*a*]phenanthrene series, the intermediate was 15-keto-15,16-dihydrocyclopenta[*a*]phenanthrene (XI), which we prepared by oxidizing the basic hydrocarbon with chromic acid, according to the procedure of Butenandt, Dannenberg, and von Dresler (6). The fact that chromic acid oxidation of cyclopenta[*a*]phenanthrene occurs at position 15 rather than at position 17 could be explained on the basis of π-electron density calculations. According to this theory, methylene groups should be the more reactive as the aromatic carbon atom to which they are attached has a higher "free-valency index" (7); in the molecule of phenanthrene, the carbon atom at position 1 is known to have a higher "free-valency index" than the carbon atom at position 2 (8). This rule might well provide a means of predicting the behavior, upon chromic acid oxidation to ketones, of compounds bearing many methyl or methylene groups.



Indolization of 15-keto-15,16-dihydrocyclopenta[*a*]phenanthrene phenylhydrazone readily yielded the hexacyclic 1′,2′:2,3-(1″,2″:6′,7′-naphthoindeno)-indole (XII). This compound is interesting for cancer research in view of the carcinogenicity of 1′,2′:2,3-indeno(4,5-benzoindole) (9).



The new compounds described here are being biologically examined in this Institute under Professor A. Lacassagne.

Acknowledgement. This work was carried out with the financial aid of the U.S. Public Health Service (Federal Security Agency); the authors wish to thank the authorities concerned.

EXPERIMENTAL[2]

Preparation of 7-keto-7,8,9,10-tetrahydroacephenanthrene. Fifty grams of β-(3-acenaphthoyl)propionic acid (m.p. 205°) was slowly heated with 80 g. of 75% hydrazine hydrate and 80 g. of potassium hydroxide in diethylene glycol (150 ml.). After all the water had been removed, the mixture was gently boiled for an additional four hours, then cooled, diluted with water, and acidified with 10% hydrochloric acid. The solid thus obtained was washed thoroughly with water, dried in a vacuum, and recrystallized from benzene. Yield, 90% of colorless γ-(3-acenaphthyl)butyric acid, m.p. 139°. Martin (10) obtained only a 50% yield of this acid by the modified Clemmensen reduction. The cyclization was conveniently effected by heating 25 g. of the acid with a mixture of sulfuric acid (90 g.) and water (30 ml.) in a boiling water-bath for 30 minutes, with frequent shaking. After cooling, the reaction product was poured into water and extracted with benzene; the benzene solution was washed with dilute sodium carbonate, then with water, and dried over sodium sulfate. After evaporation of the solvent and recrystallization of the residue from benzene, a 60% yield of ketone I was obtained. Fieser and Peters (3) reported an 87% yield by cyclizing the acid chloride with aluminum chloride, and Fieser and Hershberg (11) obtained a 78% yield by heating the acid with acetic anhydride and zinc chloride in acetic acid.

1,2-Dihydro-3',2':3,4-acenaphthenoacridine-9-carboxylic acid (VIII). A mixture of 2 g. of ketone I, 2 g. of isatin, 2.2 g. of potassium hydroxide dissolved in 3 ml. of water, and 12 ml. of ethanol, was gently refluxed for 20 hours. The reaction mixture was diluted with water and acidified with acetic acid; the precipitate obtained (3 g.) crystallized from acetic acid in fine pale yellowish needles which softened above 160°, and melted to a clear liquid at 295°. The potassium salt separated from water in almost colorless needles.

Anal. Calc'd for $C_{24}H_{17}NO_2$: N, 3.9. Found: N, 3.6.

1,2-Dihydro-3',2':3,4-acenaphthenoacridine (X). Two grams of the above cinchoninic acid was heated above the melting point and the resulting liquid distilled in a vacuum. Two recrystallizations from ethanol of the resin thus obtained yielded 1 g. of fine pale yellow needles, m.p. 141°.

Anal. Calc'd for $C_{23}H_{17}N$: C, 89.9; H, 5.5.
Found: C, 89.6; H, 5.2.

The corresponding *picrate* formed from ethanol long red needles, melting at 216° with the decomposition.

7-Bromo-1,2-dihydro-3',2':3,4-acenaphthenoacridine-9-carboxylic acid (IX). Obtained in the usual way from 0.5 g. of ketone I, 0.7 g. of 5-bromoisatin, and 0.6 g. of potassium hydroxide. Yield, 1 g. of a cinchoninic acid crystallizing from acetic acid in fine pale yellow needles, m.p. 307°.

Anal. Calc'd for $C_{24}H_{16}BrNO_2$: N, 3.2. Found: N, 3.0.

3,4-Dihydro-2',3':1,2-acenaphthenocarbazole (IIa). The crude phenylhydrazone prepared from 2 g. of ketone I and 1.5 g. of phenylhydrazine in ethanol, was indolized by two minutes' heating at 100° with 20 ml. of acetic acid saturated with hydrochloric acid. The reaction mixture was poured into water, the precipitate washed with water, and recrystallized from benzene. Yield, 2 g. of shiny colorless needles, m.p. 254°, giving with sulfuric acid an orange-yellow coloration, and a red-violet compound with picric acid.

Anal. Calc'd for $C_{22}H_{17}N$: N, 4.7. Found: N, 4.6.

[2] All melting points are uncorrected and were taken with a Maquenne block.

2',3':1,2-Acenaphthenocarbazole (IIIa). A solution of 1.8 g. of the above dihydro compound and 1.8 g. of chloranil in dry xylene (30 ml.) was gently refluxed for two hours. After cooling, the tetrachlorohydroquinone was filtered off, and washed with some xylene; the filtrate was shaken with 10% sodium hydroxide and then with water, and dried over sodium sulfate. The residue (1.5 g.) from evaporation of the xylene crystallized from toluene in fine yellowish needles melting at 276° with slight decomposition, and giving with sulfuric acid an orange-red coloration.

Anal. Calc'd for $C_{22}H_{15}N$: C, 90.1; H, 5.1.
Found: C, 89.8; H, 5.0.

6-Methyl-3,4-dihydro-2',3':1,2-acenaphthenocarbazole (IIb). The 4-tolylhydrazone obtained from 2 g. of ketone I, 3 g. of 4-tolylhydrazine hydrochloride, and 3 g. of sodium acetate in ethanol, was indolized in the usual way, yielding 2 g. of a product crystallizing from benzene in colorless needles, m.p. 261°, giving with sulfuric acid an orange-yellow coloration.

Anal. Calc'd for $C_{23}H_{19}N$: N, 4.5. Found: N, 4.3.

6-Methyl-2',3':1,2-acenaphthenocarbazole (IIIb) was prepared from 1.8 g. of the above compound and 1.9 g. of chloranil in xylene; it crystallized from xylene in fine yellow-tinged needles, m.p. 293°, with slight decomposition, giving with sulfuric acid a brown-red coloration.

Anal. Calc'd for $C_{23}H_{17}N$: C, 89.9; H, 5.5.
Found: C, 89.8; H, 5.2.

3,4-Dihydro-2',3':1,2-acenaphtheno-5,6-benzocarbazole (IV) was obtained from the β-naphthylhydrazone prepared from 2 g. of ketone I, 3 g. of β-naphthylhydrazine hydrochloride, and 3 g. of sodium acetate in ethanol; it crystallized from benzene in yellow needles (2.5 g.), m.p. 268°, giving with sulfuric acid an orange coloration.

Anal. Calc'd for $C_{26}H_{19}N$: N, 4.1. Found: N, 4.0.

2',3':1,2-Acenaphtheno-5,6-benzocarbazole (V) was prepared from 2.2 g. of chloranil in xylene; it crystallized from xylene in gray-tinged needles, melting at 315° with slight decomposition; yield, 1.5 g.

Anal. Calc'd for $C_{26}H_{17}N$: C, 90.9; H, 4.9.
Found: C, 90.5; H, 4.9.

3,4-Dihydro-2',3':1,2-acenaphtheno-7,8-benzocarbazole (VI) was obtained from the α-naphthylhydrazone prepared from 2 g. of ketone I, 3 g. of α-naphthylhydrazine hydrochloride, and 3 g. of sodium acetate. The compound crystallized from benzene in fine yellowish needles, m.p. 183°, giving with sulfuric acid a red coloration, and a violet picrate; yield, 2 g.

Anal. Calc'd for $C_{26}H_{19}N$: N, 4.1. Found: N, 4.1.

2',3':1,2-Acenaphtheno-7,8-benzocarbazole (VII) was synthesized from 1.8 g. of the above dihydro compound and 1.8 g. of chloranil; it crystallized from toluene in pale yellow needles (1 g.), m.p. 195°, giving with sulfuric acid a brownish-red coloration.

Anal. Calc'd for $C_{26}H_{17}N$: C, 90.9; H, 4.9.
Found: C, 90.8; H, 5.0.

1',2':2,3-(1'',2'':6',7'-naphthoindeno)indole (XII). The cyclopenta[*a*]phenanthrene used in this work (1 g.) was prepared by cyclization of 1-(β-1-naphthylethyl)-Δ^1-cyclopentene with aluminum chloride, and selenium dehydrogenation of the reaction product, according to Cook and Hewett (12). The chromic acid oxidation of the hydrocarbon yielded a ketone melting at 183°, in agreement with Butenandt, Dannenberg, and von Dresler (6). Half a gram of this ketone was heated with 0.3 g. of phenylhydrazine in ethanol, and the crude phenylhydrazone obtained on pouring the reaction mixture into water was treated with the usual indolization reagent. The indole crystallized from benzene in fine, almost colorless needles, m.p. 251°; yield, 0.5 g.

Anal. Calc'd for $C_{23}H_{15}N$: C, 90.4; H, 4.9.
Found: C, 90.2; H, 5.0.