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

POTENTIAL NITROGEN-HETEROCYCLE CARCINOGENS. VII. POLYCYCLIC CARBAZOLES BEARING ETHYL GROUPS, AND THIOPHENE ISOSTERS THEREOF[1]

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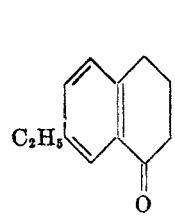
There is ample evidence that the introduction of ethyl groups into the molecule of polycyclic hydrocarbons may result in potent carcinogenic substances. Thus, according to Badger and coworkers (1), 5-ethyl-1,2-benzanthracene and 2-ethyl-3,4-benzphenanthrene readily evoke skin tumors, and Shear and Leiter (2) found 10-ethyl-1,2-benzanthracene to be a potent agent in the production of sarcomas. Similarly, 3-ethylcholanthrene (3) has been found to be fairly carcinogenic, though less than the lower homolog.

In the field of experimental inhibition of tumor-growth by chemical compounds, the activity of some ethyl derivatives has also been recorded (4), and it is of interest to note that in one instance (2-ethyl-3,4-benzphenanthrene), the ethyl compound was found considerably more active than the methyl homolog.

These considerations led us to the preparation, for biological experimentation, of various polycyclic carbazoles bearing ethyl radicals; some thiophene compounds isosteric with the latter were also included in this study.

The modified Fischer-Borsche synthesis of carbazoles as described in previous



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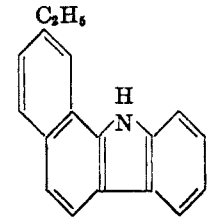

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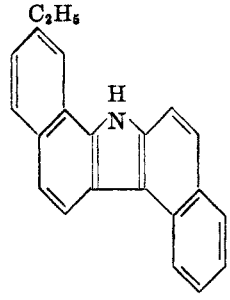

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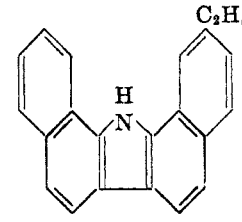
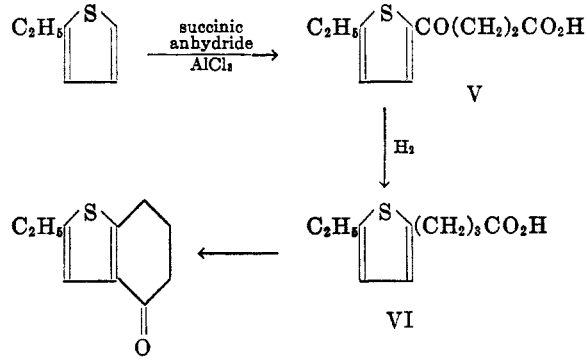


IV

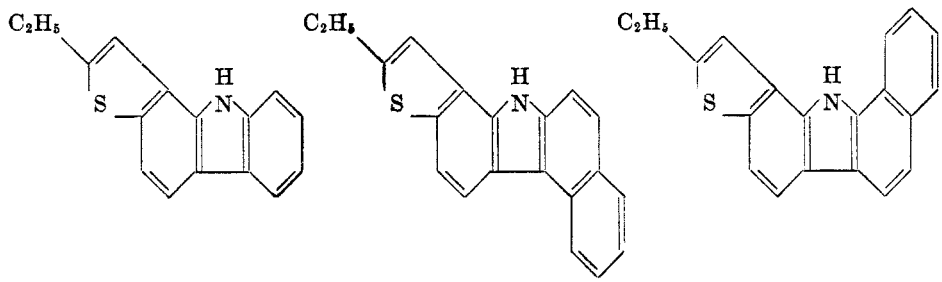
[1] Paper VI in this series: Buu-Hoï, Cagniant, Hoán, and Khôi, *J. Org. Chem.*, preceding article.

papers of this series, could readily be applied to the known 7-ethyl-1-tetralone (I). Thus were obtained, *via* the corresponding 3,4-dihydro compounds: 2′-ethyl-1,2-benzocarbazole (II), 2′-ethyl-1,2,5,6-dibenzocarbazole (III), and 2′-ethyl-1,2,7,8-dibenzocarbazole (IV).

In the thiophene series, 2-ethyl-4-keto-4,5,6,7-tetrahydrothianaphthene (VII), a previously unknown compound, was prepared as follows: succinoylation of 2-ethylthiophene (readily prepared from 2-acetothienone hydrazone by means of the Wolff-Kishner method), reduction of β-(2-ethyl-5-thenoyl)propionic acid (V) to γ-(2-ethyl-5-thienyl)butyric acid (VI) through the same reaction, and cyclization of γ-(2-ethyl-5-thienyl)butyryl chloride by means of stannic chloride.



2-Ethyl-4-keto-4,5,6,7-tetrahydrothianaphthene readily underwent carbazole syntheses, and thus were obtained, *via* the corresponding dihydro compounds: 5′-ethyl-3′,2′:1,2-thiophenocarbazole (VIII), 5′-ethyl-3′,2′:1,2-thiopheno-5,6-benzocarbazole (IX), and 5′-ethyl-3′,2′:1,2-thiopheno-7,8-benzocarbazole (X).



VIII IX X

The new compounds described here are under biological examination by Professor A. Lacassagne.

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EXPERIMENTAL[2]

2-Acetothienone. Several methods for the preparation of this compound have recently been proposed (5); we found the following modification of the Biedermann procedure (6) especially convenient: into an ice-cooled solution of 170 g. of thiophene (2 moles) and 173 g. of acetyl chloride (2.1 moles) in one liter of dry carbon disulphide, 300 g. of finely powdered aluminum chloride was stirred in small portions. Stirring was continued for one hour at room temperature, and the mixture was poured onto ice; the organic layer was washed with small portions of a dilute aqueous solution of sodium hydroxide and then with a little water, dried over sodium sulfate, the solvent distilled off, and the residue fractionated. Yield: 80–85%.

2-Ethylthiophene. This compound has been prepared by means of the Wurtz-Fittig reaction (7), by the Clemmensen reduction of 2-acetothienone (8), and recently by the Wolff-Kishner reduction of 2-acetothienone hydrazone in ethylene glycol medium (9). We found the following adaptation of Huang-Minlon's general technique (10) to be very convenient, and it could be extended to various thiophene ketones: a mixture of 2-acetothienone (50 g.) 50% hydrazine hydrate (50 g.), potassium hydroxide (35 g.), and diethylene glycol (200 ml.) was slowly heated up to 185–190° in a flask fitted with a fractionating-column. The distillate was collected, washed with dilute hydrochloric acid, then with water, dried over calcium chloride, and fractionated; 38 g. (80%) of 2-ethylthiophene were obtained, b.p. 134–135°.

β-(2-Ethyl-5-thenoyl)propionic acid (V). Into an ice-cooled mixture of 2-ethylthiophene (56 g.), succinic anhydride (56 g.), and nitrobenzene (350 ml.), finely powdered aluminum chloride (150 g.) was stirred in small portions. After 16 hours at room temperature, the mixture was poured onto ice, and the nitrobenzene was removed by steam-distillation. After cooling, the solid product was purified by dissolution in aqueous sodium carbonate and reprecipitation with dilute hydrochloric acid (yield, 97 g.). After crystallization from toluene, fine colorless needles m.p. 96° were obtained.

Anal. Calc'd for $C_{10}H_{12}O_3S$: C, 56.6; H, 5.6.
Found: C, 56.3; H, 5.8.

γ-(2-Ethyl-5-thienyl)butyric acid (VI). A mixture of the foregoing acid (90 g.), 75% hydrazine hydrate (90 g.), potassium hydroxide (80 g.), and diethylene glycol (300 ml.) was heated, and water removed until the temperature reached 190–195°; the greater part of the solvent then was removed in a vacuum. The residue was dissolved in water and acidified with dilute hydrochloric acid. The reaction-product was extracted with ether and the ether solution dried over calcium chloride. After removal of the solvent, vacuum-distillation of the residue yielded 46 g. of the acid (VI) in the form of a fluid, pale green-yellow oil, b.p. 190–192°/18 mm.

Anal. Calc'd for $C_{10}H_{14}O_2S$: C, 65.5; H, 7.7.
Found: C, 65.5; H, 7.9.

γ-(2-Ethyl-5-thienyl)butyryl chloride. A mixture of the foregoing acid (46 g.), freshly redistilled thionyl chloride (33 g.), and anhydrous ether (100 ml.) was gently refluxed for four hours with 12 drops of pyridine. The solvent and the excess of thionyl chloride were removed in a vacuum, and the residue fractionated. Yield, 50 g. of a pale yellow, fluid oil, b.p. 167–174°/18 mm.

Anal. Calc'd for $C_{10}H_{13}ClOS$: C, 55.4; H, 6.0.
Found: C, 55.2; H, 6.3.

2-Ethyl-4-keto-4,5,6,7-tetrahydrothianaphthene (VII). To an ice-cooled solution of the foregoing chloride (49 g.) in carbon disulfide (150 ml.), was added dropwise with stirring a solution of stannic chloride (80 g.) in carbon disulfide (300 ml.). After the addition, the mixture was gently refluxed for two hours, then poured onto ice and some ether added. The organic layer was washed with water, dried over sodium sulfate, the solvents removed and the residue vacuum-fractionated. Yield, 98% of a pale yellow liquid *ketone*, b.p. 161°/16 mm.

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

Anal. Calc'd for $C_{16}H_{12}OS$: C, 66.6; H, 6.6.
Found: C, 66.5; H, 6.8.

The corresponding *semicarbazone* formed (from methanol) fine colorless shiny needles m.p. 219°.

7-Ethyl-1-tetralone (I). This compound was obtained according to Bachmann and Edgerton (11), except that β-(4-ethylbenzoyl)propionic acid (prepared in benzene) was reduced as follows by means of the Wolff-Kishner—Huang-Minlon method: a mixture of that crude acid (70 g.), 75% hydrazine hydrate (70 g.), potassium hydroxide (80 g.), and diethylene glycol (200 ml.) was heated to 190–195° with removal of water, most of the solvent vacuum-distilled, and the residue treated in the usual way. Yield, 50 g. of *γ-(4-ethylphenyl)butyric acid*, b.p. 200°/20 mm., melting at 68° after crystallization from ligroin.

2'-Ethyl-3,4-dihydro-1,2-benzocarbazole. Obtained by indolization of the phenylhydrazone of ketone I in the previously described way (12); formed (from petroleum ether) colorless microcrystalline prisms, m.p. 110°.

Anal. Calc'd for $C_{18}H_{17}N$: N, 5.6. Found: N, 5.9.

2'-Ethyl-1,2-benzocarbazole (II). Obtained by refluxing a xylene solution of the *dihydro* compound (1.5 g.) with chloranil (1.6 g.) for three hours, removing the tetrachlorohydroquinone formed with aqueous sodium hydroxide, and crystallizing the residue from a mixture of benzene and ligroin. Yield, 1.2 g. of gray-tinged shiny prisms, m.p. 142°; sulfuric acid produced a greenish coloration, rapidly turning blue.

Anal. Calc'd for $C_{18}H_{15}N$: N, 5.7. Found: N, 5.5.

2'-Ethyl-3,4-dihydro-1,2,5,6-dibenzocarbazole. From the β-naphthylhydrazone of ketone I; formed (from a mixture of benzene and ligroin) gray-tinged microscopic needles, m.p. 173°. Orange-red coloration with sulfuric acid, turning green.

Anal. Calc'd for $C_{22}H_{19}N$: N, 4.7. Found: N, 4.6.

2'-Ethyl-1,2,5,6-dibenzocarbazole (III). Crystallized from benzene in gray-tinged microscopic needles, m.p. 190°, giving with sulfuric acid a blood red coloration.

Anal. Calc'd for $C_{22}H_{17}N$: N, 4.7. Found: N, 4.5.

2'-Ethyl-3,4-dihydro-1,2,7,8-dibenzocarbazole. From the α-naphthylhydrazone of ketone I; formed (from ligroin) colorless microcrystals, m.p. 109°, giving with sulfuric acid an orange-red coloration, turning green.

Anal. Calc'd for $C_{22}H_{19}N$: N, 4.7. Found: N, 4.8.

2'-Ethyl-1,2,7,8-dibenzocarbazole (IV). Formed (from ligroin) colorless microcrystals, m.p. 121°, giving with sulfuric acid a blood red coloration.

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

5'-Ethyl-3,4-dihydro-3',2':1,2-thiophenocarbazole. Obtained by smooth indolization of the phenylhydrazone of ketone VII, formed (from benzene) cream microscopic prisms, m.p. 125°.

Anal. Calc'd for $C_{16}H_{15}NS$: N, 5.5. Found: N, 5.3.

5'-Ethyl-3',2':1,2-thiophenocarbazole (VIII). Formed (from benzene) gray-tinged microcrystals, m.p. 187°; the *picrate* is violet.

Anal. Calc'd for $C_{16}H_{13}NS$: N, 5.6. Found: N, 5.4.

5'-Ethyl-3,4-dihydro-3',2':1,2-thiopheno-5,6-benzocarbazole. From the β-naphthylhydrazone of ketone VII; crystallized from benzene in shiny colorless needles, m.p. 175°, giving with sulfuric acid a red coloration.

Anal. Calc'd for $C_{20}H_{17}NS$: N, 4.8. Found: N, 4.9.

5'-Ethyl-3',2':1,2-thiopheno-5,6-benzocarbazole (IX). Formed (from benzene) shiny colorless needles, m.p. 209°, giving with sulfuric acid a brown-red coloration.

Anal. Calc'd for $C_{20}H_{15}NS$: N, 4.8. Found: N, 4.6.

5'-Ethyl-3,4-dihydro-3',2':1,2-thiopheno-7,8-benzocarbazole. From the α-naphthylhydrazone of ketone VII; formed (from benzene) cream microneedles, m.p. 140°.

Anal. Calc'd for $C_{20}H_{17}NS$: N, 4.8. Found: N, 4.6.

5'-Ethyl-3',2':1,2-thiopheno-7,8-benzocarbazole (X). Formed (from benzene) gray-tinged needles, m.p. 170°; red coloration with sulfuric acid.

Anal. Calc'd for $C_{20}H_{15}NS$: N, 4.8. Found: N, 4.6.

SUMMARY

1. The synthesis of 2-ethyl-4-keto-4,5,6,7-tetrahydrothianaphthene is reported.

2. From that ketone and from its isolog, 7-ethyl-1-tetralone, several new polycyclic carbazoles were prepared.

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