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

POTENTIAL NITROGEN-HETEROCYCLE CARCINOGENS. IX. HALOGEN-CONTAINING ANGULAR BENZO- AND DIBENZO-CARBAZOLES, AND THEIR THIOPHENE ANALOGS

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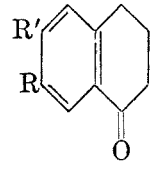
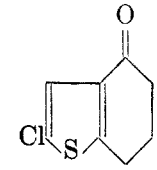
The influence upon the biological activity of the introduction of halogen atoms in the molecules of polycyclic carcinogens has heretofore been but scantily investigated. In the 1,2-benzanthracene series, the 5-, 7-, and 6-chloro-10-methyl derivatives synthesized by Newman (1) and Newman and Orchin (2) have been tested by Shear and Leiter (3), and the two first found to be carcinogenic; 9,10-dichloro-1,2-benzanthracene has been found by Lacassagne, Buu-Hoï, and Hoán (4) to be very feebly so. In the benzacridine group, several chlorine-containing derivatives (5) are still undergoing biological testing.

In the field of angular benzo- and dibenzo-carbazoles, no such studies have yet been made, and the present paper gives account of the preparation of a series of chlorine- and bromine-containing 1,2-benzocarbazoles, and 1,2:5,6- and 1,2:7,8-dibenzocarbazoles.



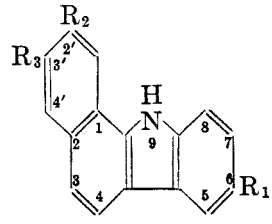
I R = Cl, R′ = H
II R = Br, R′ = H
III R = OCH_3, R′ = Cl



XXII

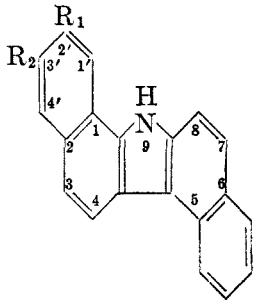
The method of synthesis used was the Fischer-Borsche indole ring-closure of arylhydrazones of properly substituted 1-tetralones, followed by chloranil dehydrogenation of the polycyclic 3,4-dihydrocarbazoles thus obtained. The tetralones used in this work were: 7-chloro- (I), 7-bromo- (II), and 6-chloro-7-methoxy-1-tetralone (III); all had been described previously in the literature, but some modifications have now been introduced in their preparation. The arylhydrazines involved were phenyl-, 4-tolyl-, and 4-bromophenyl-hydrazine, and α- and β-naphthylhydrazine. In the case of carbazoles bearing a methoxyl group, treatment with pyridine hydrochloride readily gave the corresponding carbazoles with free phenolic hydroxyl groups.

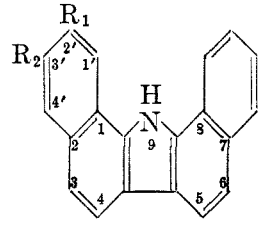
The new carbazoles thus synthesized were:



IV $R_1 = R_3 = H, R_2 = Cl$
V $R_1 = R_3 = H, R_2 = Br$
VI $R_1 = CH_3, R_2 = Cl, R_3 = H$
VII $R_1 = CH_3, R_2 = Br, R_3 = H$
VIII $R_1 = Br, R_2 = Cl, R_3 = H$
IX $R_1 = H, R_2 = OCH_3, R_3 = Cl$
X $R_1 = H, R_2 = OH, R_3 = Cl$
XI $R_1 = Br, R_2 = OCH_3, R_3 = Cl$
XII $R_1 = Br, R_2 = OH, R_3 = Cl$

(a) *in the 1,2-benzocarbazole series:* 2′-chloro- (IV), 2′-bromo- (V), 2′-chloro-6-methyl- (VI), 2′-bromo-6-methyl(VII), 6-bromo-2′-chloro- (VIII), 3′-chloro-2′-methoxy- (IX), 3′-chloro-2′-hydroxy- (X), 6-bromo-3′-chloro-2′-methoxy- (XI), and 6-bromo-3′-chloro-2′-hydroxy-1,2-benzocarbazole (XII).

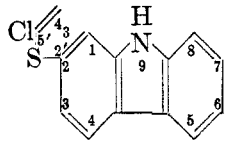




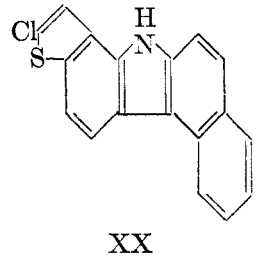
XIII	R_1 = Cl,	R_2 = H		XVI	R_1 = Cl,	R_2 = H
XIV	R_1 = Br,	R_2 = H		XVII	R_1 = Br,	R_2 = H
XV	R_1 = OCH_3,	R_2 = Cl		XVIII	R_1 = OCH_3,	R_2 = Cl
XVa	R_1 = OH,	R_2 = Cl		XVIIIa	R_1 = OH,	R_2 = Cl

(b) *in the 1,2:5,6-dibenzocarbazole series:* 2′-chloro- (XIII), 2′-bromo- (XIV) and 3′-chloro-2′-methoxy-1,2:5,6-dibenzocarbazole (XV) and the corresponding phenol (XVa).

(c) *in the 1,2:7,8-dibenzocarbazole series:* 2′-chloro- (XVI), 2′-bromo- (XVII), and 3′-chloro-2′-methoxy-1,2:7,8-dibenzocarbazole (XVIII) and the corresponding phenol (XVIIIa).



XIX



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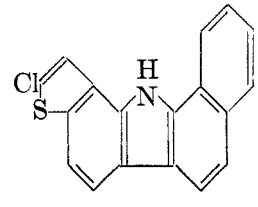

XXI

In view of the widespread biological similarity between the benzene and the thiophene nucleus, 5′-chloro-3′,2′:1,2-thiophenocarbazole (XIX), 5′-chloro-3′,2′:1,2-thiopheno-5,6-benzocarbazole (XX), and 5′-chloro-3′,2′:1,2-thiopheno-7,8-benzocarbazole (XXI) were also prepared for parallel biological testing along with their respective isosteres IV, XIII, and XVI. Their synthesis started from 2-chloro-4-keto-4,5,6,7-tetrahydrothianaphthene (XXII) and followed the usual pattern.

The new substances reported here are under biological examination in this Institute by Professor Lacassagne and Dr. Zajdela.

Acknowledgement. This work has been carried out under a grant from the U. S. Public Health Service (Federal Security Agency); the authors wish to express their gratitude to the authorities concerned.

EXPERIMENTAL

Preparation of intermediates. Ketones I, XXII, II, and III were prepared from chlorobenzene, 2-chlorothiophene, bromobenzene, and *o*-chloroanisole, respectively, by means of the routine succinic anhydride method. 7-Chloro-1-tetralone had previously been prepared by von Braun (6) by a Sandmeyer reaction on the corresponding amino compound. 7-Bromo-1-tetralone had previously been described by Fieser and Seligman (7), and 6-chloro-7-methoxy-1-tetralone by Hoán and Buu-Hoï (8). In the present work, the reduction of β-4-chloro- and β-4-bromo-benzoylpropionic acid, β-(3-chloro-4-methoxybenzoyl)propionic acid, and β-(5-chloro-2-thenoyl)propionic acid was achieved by means of the Wolff-Kishner method as modified by Huang-Minlon (9), the yields throughout being far better than with the Clemmensen reduction.

General observations upon carbazole syntheses. In the following syntheses, the arylhydrazones of the various 1-tetralones were prepared by refluxing the ketone with an arylhydrazine hydrochloride in ethanol and in the presence of sodium acetate. The crude arylhydrazone obtained on pouring the reaction mixture into ice-water was collected, dried rapidly *in vacuo*, and indolized without further purification, in view of the ready oxidizability of these substances. The yields of these indolizations were very good (80–90%) with tetralones of the benzene series, but were far less satisfactory (30–40%) in the thiophene series. With the latter, a considerable evolution of hydrogen sulfide accompanied the cyclization, especially on prolonged heating. Chloranil dehydrogenations were effected with equally high yields (70–80%) in both the benzene and the thiophene series.

2'-Chloro-3,4-dihydro-1,2-benzocarbazole was obtained in quantitative yield by a short heating of the crude phenylhydrazone of ketone I with our usual indolization-reagent (acetic acid saturated with dry hydrogen chloride). The compound separated from benzene as colorless needles, m.p. 145°, giving an orange-yellow coloration with sulfuric acid.

Anal. Calc'd for $C_{16}H_{12}ClN$: N, 5.6. Found: N, 5.6.

2'-Chloro-1,2-benzocarbazole (IV) was obtained in the usual way from the dihydro compound (1 g.) and chloranil (1.1 g.) in boiling xylene; it crystallized from benzene as shiny colorless leaflets, m.p. 208°.

Anal. Calc'd for $C_{16}H_{10}ClN$: C, 76.3; H, 3.9.
Found: C, 76.0; H, 4.1.

2'-Bromo-3,4-dihydro-1,2-benzocarbazole was prepared from the phenylhydrazone of ketone II; it crystallized from a mixture of benzene and ligroin in colorless prisms, m.p. 133°, giving a yellow coloration with sulfuric acid.

Anal. Calc'd for $C_{16}H_{12}BrN$: N, 4.7. Found: N, 4.5.

2'-Bromo-1,2-benzocarbazole (V) separated from benzene in shiny colorless leaflets, m.p. 213°.

Anal. Calc'd for $C_{16}H_{10}BrN$: N, 4.7. Found: N, 4.6.

2'-Chloro-6-methyl-3,4-dihydro-1,2-benzocarbazole was obtained from the 4-tolylhydrazone of ketone I; it separated from benzene as shiny colorless leaflets, m.p. 170°, giving an orange-yellow coloration with sulfuric acid.

Anal. Calc'd for $C_{17}H_{14}ClN$: N, 5.2. Found: N, 5.0.

2'-Chloro-6-methyl-1,2-benzocarbazole (VI) crystallized from benzene as shiny colorless leaflets, m.p. 227°.

Anal. Calc'd for $C_{17}H_{12}ClN$: C, 76.8; H, 4.5.
Found: C, 76.7; H, 4.8.

2'-Bromo-6-methyl-3,4-dihydro-1,2-benzocarbazole was prepared from the 4-tolylhydrazone of ketone II; it separated from benzene as microscopic colorless needles, m.p. 178°.

Anal. Calc'd for $C_{17}H_{14}BrN$: N, 4.4. Found: N, 4.1.

2'-Bromo-6-methyl-1,2-benzocarbazole (VII) separated from xylene as colorless prisms, m.p. 236°, giving an orange coloration with sulfuric acid.

Anal. Calc'd for $C_{17}H_{12}BrN$: N, 4.5. Found: N, 4.3.

6-Bromo-2'-chloro-3,4-dihydro-1,2-benzocarbazole, obtained from the 4-bromophenylhydrazone of ketone I, crystallized from a mixture of benzene and ligroin as fine colorless needles, m.p. 120°.

Anal. Calc'd for $C_{16}H_{11}BrClN$: N, 4.2. Found: N, 4.0.

6-Bromo-2'-chloro-1,2-benzocarbazole (VIII) separated from benzene as shiny colorless leaflets, m.p. 201°, giving a yellow coloration with sulfuric acid.

Anal. Calc'd for $C_{16}H_9BrClN$: C, 58.0; H, 2.7.
Found: C, 57.7; H, 3.0.

2',6-Dibromo-3,4-dihydro-1,2-benzocarbazole, prepared from the 4-bromophenylhydrazone of ketone II, separated from ligroin as fine colorless needles, m.p. 120°.

Anal. Calc'd for $C_{16}H_{11}Br_2N$: N, 3.7. Found: N, 3.5.

3'-Chloro-2'-methoxy-3,4-dihydro-1,2-benzocarbazole was obtained from the phenylhydrazone of ketone III; it crystallized from benzene as colorless needles, m.p. 210–211°, giving a yellow coloration with sulfuric acid.

Anal. Calc'd for $C_{17}H_{14}ClNO$: N, 4.9. Found: N, 4.6.

3'-Chloro-2'-methoxy-1,2-benzocarbazole (IX) separated from benzene as shiny colorless leaflets, m.p. 236°, subliming above 210°.

Anal. Calc'd for $C_{17}H_{12}ClNO$: C, 72.4; H, 4.2.
Found: C, 72.2; H, 4.5.

2'-Chloro-2'-hydroxy-1,2-benzocarbazole (X). A mixture of 1 g. of the above compound with 10 g. of redistilled pyridine hydrochloride was refluxed for ten minutes; the precipitate obtained on treatment with water was dried and recrystallized from benzene. It formed fine colorless needles, m.p. 191°, giving a yellow coloration with sulfuric acid.

Anal. Calc'd for $C_{16}H_{10}ClNO$: N, 5.2. Found: N, 5.0.

6-Bromo-3'-chloro-2'-methoxy-3,4-dihydro-1,2-benzocarbazole was obtained from the 4-bromophenylhydrazone of ketone III; it crystallized from benzene in colorless needles, m.p. 220°.

Anal. Calc'd for $C_{17}H_{13}BrClNO$: N, 3.8. Found: N, 3.9.

6-Bromo-3'-chloro-2'-methoxy-1,2-benzocarbazole (XI) separated from benzene as colorless needles, m.p. 254°, subliming easily above 220°.

Anal. Calc'd for $C_{17}H_{11}BrClNO$: C, 56.6; H, 3.0.
Found: C, 56.3; H, 3.2.

6-Bromo-3'-chloro-2'-hydroxy-1,2-benzocarbazole (XII) crystallized from benzene as almost colorless needles, m.p. 259°, soluble in aqueous sodium hydroxide.

Anal. Calc'd for $C_{16}H_9BrClNO$: N, 4.0. Found: N, 4.0.

2'-Chloro-3,4-dihydro-1,2:5,6-dibenzocarbazole, prepared from the β-naphthylhydrazone of ketone I, crystallized from benzene as yellow-tinged needles, m.p. 185°, giving an orange coloration with sulfuric acid.

Anal. Calc'd for $C_{20}H_{14}ClN$: N, 4.6. Found: N, 4.5.

2'-Chloro-1,2:5,6-dibenzocarbazole (XIII) separated from xylene as iridescent colorless leaflets, m.p. 237°, giving an orange-red coloration with sulfuric acid.

Anal. Calc'd for $C_{20}H_{12}ClN$: C, 79.6; H, 3.9.
Found: C, 79.3; H, 4.0.

2'-Bromo-3,4-dihydro-1,2:5,6-dibenzocarbazole, obtained from the β-naphthylhydrazone of ketone II crystallized from a mixture of benzene and ligroin as yellowish crystals, m.p. 204°.

Anal. Calc'd for $C_{20}H_{14}BrN$: N, 4.0. Found: N, 3.8.

2'-Bromo-1,2:5,6-dibenzocarbazole (XIV) separated from xylene as gray needles, m.p. 248°, giving a brown-red coloration with sulfuric acid.

Anal. Calc'd for $C_{20}H_{12}BrN$: C, 69.4; H, 3.5.
Found: C, 69.2; H, 3.8.

3'-Chloro-2'-methoxy-3,4-dihydro-1,2:5,6-dibenzocarbazole was prepared from the β-naphthylhydrazone of ketone III; it crystallized from benzene as colorless leaflets, m.p. 274°, giving an orange coloration with sulfuric acid.

Anal. Calc'd for $C_{21}H_{16}ClNO$: N, 4.2. Found: N, 4.1.

3'-Chloro-2'-methoxy-1,2:5,6-dibenzocarbazole (XV) was obtained, after recrystallization from xylene and subsequent vacuum-sublimation, as shiny colorless needles, m.p. 311°, giving a brown-red coloration with sulfuric acid.

Anal. Calc'd for $C_{21}H_{14}ClNO$: C, 76.0; H, 4.2.
Found: C, 76.2; H, 4.1.

3'-Chloro-2'-hydroxy-1,2:5,6-dibenzocarbazole (XVa) separated from xylene as shiny colorless needles, m.p. 254°, giving a red coloration with sulfuric acid.

Anal. Calc'd for $C_{20}H_{12}ClNO$: N, 4.4. Found: N, 4.2.

2'-Chloro-3,4-dihydro-1,2:7,8-dibenzocarbazole, obtained from the α-naphthylhydrazone of ketone I separated from ligroin as gray-tinged leaflets, m.p. 172°, giving a deep-red coloration with sulfuric acid.

Anal. Calc'd for $C_{20}H_{14}ClN$: N, 4.6. Found: N, 4.5.

2'-Chloro-1,2:7,8-dibenzocarbazole (XVI) crystallized from xylene in colorless leaflets, m.p. 235°.

Anal. Calc'd for $C_{20}H_{12}ClN$: C, 79.6; H, 4.0.
Found: C, 79.5; H, 4.3.

2'-Bromo-3,4-dihydro-1,2:7,8-dibenzocarbazole was prepared from the α-naphthylhydrazone of ketone II; it separated from benzene as gray-tinged needles, m.p. 184°, giving an orange color with sulfuric acid.

Anal. Calc'd for $C_{20}H_{14}BrN$: N, 4.0, Found: N, 3.8.

2'-Bromo-1,2:7,8-dibenzocarbazole (XVII) crystallized from toluene in colorless leaflets, m.p. 231°, giving a red coloration with sulfuric acid.

Anal. Calc'd for $C_{20}H_{12}BrN$: C, 69.4; H, 3.5.
Found: C, 69.5; H, 3.6.

3'-Chloro-2'-methoxy-3,4-dihydro-1,2:7,8-dibenzocarbazole was obtained from the α-naphthylhydrazone of ketone III; it crystallized from benzene as colorless needles, m.p. 217°.

Anal. Calc'd for $C_{21}H_{16}ClNO$: N, 4.2. Found: N, 4.1.

3'-Chloro-2'-methoxy-1,2:7,8-dibenzocarbazole (XVIII) separated from benzene as shiny colorless needles, m.p. 243°, giving a red coloration with sulfuric acid.

Anal. Calc'd for $C_{21}H_{14}ClNO$: C, 76.0; H, 4.2.
Found: C, 75.7; H, 4.4.

3'-Chloro-2'-hydroxy-1,2:7,8-dibenzocarbazole (XVIIIa) crystallized from xylene in shiny colorless needles, m.p. 328°, giving a red coloration with sulfuric acid.

Anal. Calc'd for $C_{20}H_{12}ClNO$: N, 4.4. Found: N, 4.3.

5'-Chloro-3,4-dihydro-3',2':12-thiophenocarbazole was obtained from the phenylhydrazone of ketone XXII by cyclization at 60°, extensive decomposition with liberation of hydrogen sulfide occurring on prolonged heating; it separated from a mixture of benzene and ligroin as fine colorless needles, m.p. 130°.

Anal. Calc'd for $C_{14}H_{10}ClNS$: N, 5.4. Found: N, 5.3.

5'-Chloro-3',2':1,2-thiophenocarbazole (XIX) crystallized from benzene in shiny colorless leaflets, m.p. 210°. It gave a yellow coloration with sulfuric acid.

Anal. Calc'd for $C_{14}H_8ClNS$: C, 65.2; H, 3.1.
Found: C, 65.0; H, 3.4.

5'-Chloro-3,4-dihydro-3',2':1,2-thiopheno-5,6-benzocarbazole was obtained from the β-naphthylhydrazone of ketone XXII; it crystallized from benzene in yellow needles, m.p. 181°.

Anal. Calc'd for $C_{18}H_{12}ClNS$: N, 4.5. Found: N, 4.3.

5'-Chloro-3',2'-thiopheno-5,6-benzocarbazole (XX) crystallized from benzene as gray-tinged needles, m.p. 227°. The compound gave a brown coloration with sulfuric acid.

Anal. Calc'd for $C_{18}H_{16}ClNS$: C, 70.2; H, 3.3.
Found: C, 71.9; H, 3.5.

5'-Chloro-3',2':1,2-thiopheno-7,8-benzocarbazole (XXI). The corresponding *3,4-dihydro* compound obtained by indolization of the α-naphthylhydrazone of ketone XXII crystallized from ligroin as yellowish needles, m.p. 106°, and yielded on dehydrogenation the expected carbazole, crystallizing from benzene in grayish needles, m.p. 206°. It gave a deep red coloration with sulfuric acid.

Anal. Calc'd for $C_{14}H_8ClNS$: C, 65.2; H, 3.1.
Found: C, 65.5; H, 3.0.

SUMMARY

1. A series of new halogen-containing 1,2-benzocarbazoles and 1,2:5,6- and 1,2:7,8-dibenzocarbazoles prepared for biological testing, are described.

2. Several thiophene isosteres of these compounds have been prepared for parallel biological study.

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