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

CARCINOGENIC DERIVATIVES OF CARBAZOLE. I. THE SYNTHESIS OF 1,2,7,8-, 1,2,5,6-, AND 3,4,5,6-DIBENZOCARBAZOLE AND SOME OF THEIR DERIVATIVES[1]

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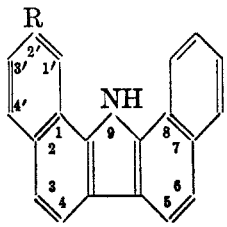
1,2,7,8-, (I, R = H), 1,2,5,6-, (II, R = H), and 3,4,5,6-dibenzocarbazole (III) play an important role in the chemistry of cancer, both on account of their activity in promoting malignant growths in various organs (1) and of their presumed endogenous formation from certain carcinogenic azo compounds of the naphthalene series (2).



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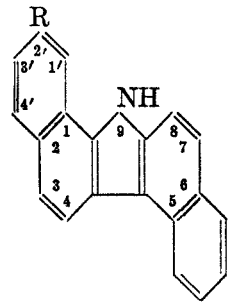

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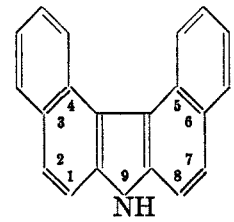

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1,2,5,6-Dibenzocarbazole has also been found to possess considerable inhibitory powers against the growth of Walker rat carcinoma (3). This provided an incentive to the study of the relationship between substitution and carcinogenicity or growth-inhibitory powers in this series, and general methods for the synthesis of bis-angular dibenzocarbazoles have therefore been more thoroughly investigated.

The procedure most commonly used hitherto for preparing these three dibenzocarbazoles is based upon the Bucherer reaction. This consists in the heating of sodium bisulfite and α- or β-naphthylhydrazine, alone in the case of 1,2,7,8- and 3,4,5,6-dibenzocarbazole, or with 3-hydroxy-2-naphthoic acid in the case of 1,2,5,6- and 3,4,5,6-dibenzocarbazole (4). However, because of the relative inaccessibility of substituted naphthylhydrazines, this method is hardly feasible for the synthesis of functional derivatives and homologs of dibenzocarbazoles.

The deamination by mineral acids of o,o'-diamines obtained in the benzidine rearrangement of hydrazonaphthalenes has been used for the preparation of 1,2,7,8-dibenzocarbazole by Nietzski and Goll (5), of 3,4,5,6-dibenzocarbazole by Meisenheimer and Witte (6), and, more recently, of 1,2,5,6-dibenzocarbazole

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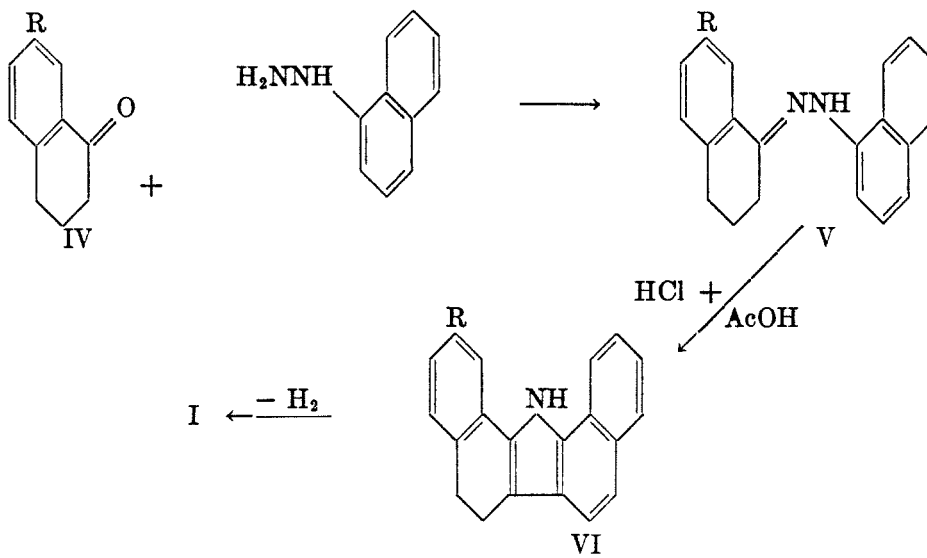
by Warren (7). An extension of this procedure to the preparation of substituted dibenzocarbazoles is also precluded by reason of the inaccessibility of *o,o'*-diamines with ascertained constitution, in the naphthalene series.

The Japp-Maitland procedure (8) which involves the heating at high temperature of naphthols with naphthylhydrazines and naphthylhydrazine hydrochlorides gives extremely low yields, since naphthylhydrazines and their salts are highly sensitive to heat.

We have now found that the Fischer-Borsche synthesis of indoles and carbazoles (9), when applied to naphthylhydrazines and tetralones, permitted the easy preparation of the three bis-angular dibenzocarbazoles and of a series of their homologs and functional derivatives.

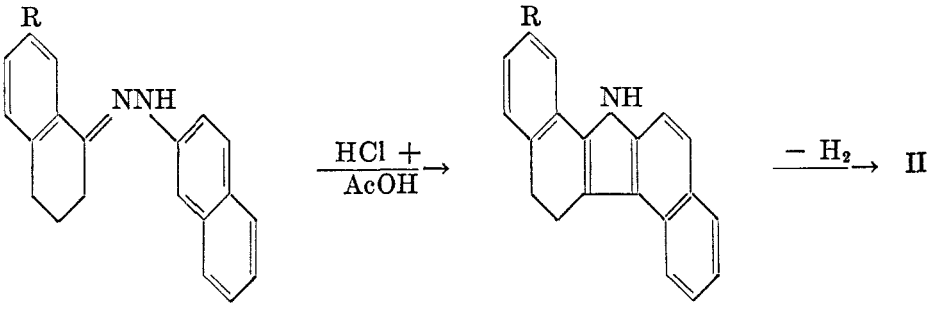
1,2,7,8-Dibenzocarbazole series. Under the influence of a solution of dry hydrochloric acid in glacial acetic acid, tetralone-1-α-naphthylhydrazone (V, R = H) readily underwent cyclization into 3,4-dihydro-1,2,7,8-dibenzocarbazole



(VI, R = H); this was easily dehydrogenated into 1,2,7,8-dibenzocarbazole (I) by means of chloranil, a reagent recommended by Barclay and Campbell (10) for the dehydrogenation of tetrahydrocarbazoles, after Arnold, *et al.* (11) had used it with success for the preparation of various aromatic hydrocarbons.

The replacement of tetralone-1 in the above synthesis by 7-nitrotetralone-1 (IV, R = NO_2, obtained as the main product in the nitration of tetralone-1), yielded 2'-nitro-1,2,7,8-dibenzocarbazole (I, R = NO_2) *via* 2'-nitro-3,4-dihydro-1,2,7,8,-dibenzocarbazole (VI, R = NO_2), which underwent spontaneous dehydrogenation on being heated above its melting point. 7-Methoxytetralone-1 (IV, R = OCH_3, conveniently prepared from anisole by means of the routine succinic anhydride procedure) gave similarly 2'-methoxy-1,2,7,8-dibenzocarbazole (I, R = OCH_3) *via* the corresponding 3,4-dihydro derivative (VI, R = OCH_3).

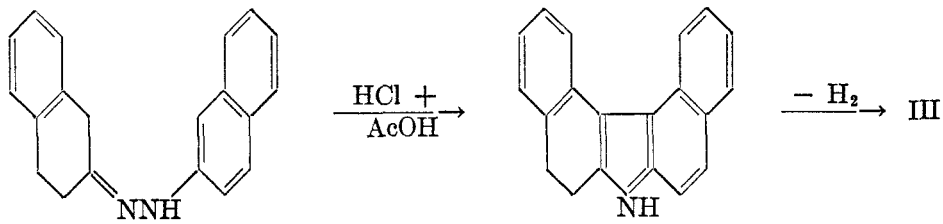
1,2,5,6-Dibenzocarbazole series. Owing to the outstanding physiological properties of 1,2,5,6-dibenzocarbazole, many more compounds in this group have been prepared. The syntheses which involved β-naphthylhydrazone followed a similar pattern as for the preceding series, tetralone-1 β-naphthylhydrazone (VII, R = H) being cyclized into 3,4-dihydro-1,2,5,6-dibenzo-



VII VIII

carbazole (VIII, R = H), and the latter dehydrogenated with chloranil. In the preparation of 2′-nitro-1,2,5,6-dibenzocarbazole (II, R = NO_2) from 7-nitrotetralone-1 β-naphthylhydrazone (VII, R = NO_2), the intermediary dihydro compound (VIII, R = NO_2) lost a molecule of hydrogen so easily that it could not be isolated. 7-Methyltetralone-1 (IV, R = CH_3) and 7-*ter*-butyltetralone-1 (IV, R = *ter*-C_4H_9), prepared from toluene and *ter*-butylbenzene by the succinic anhydride method, gave respectively 2-methyl-, (II, R = CH_3) and 2′-*ter*-butyl-1,2,5,6-dibenzocarbazole (II, R = *ter*-C_4H_9) *via* the stable corresponding 3,4-dihydro derivatives. From 7-methoxytetralone-1,2′-methoxy-1,2,-5,6-dibenzocarbazole (II, R = OCH_3) was similarly obtained *via* 2′-methoxy-3,4-dihydro-1,2,5,6-dibenzocarbazole (VIII, R = OCH_3).

3,4,5,6-Dibenzocarbazole. This compound was readily prepared from tetralone-2 β-naphthylhydrazone, the intermediary 1,2-dihydro-3,4,5,6-dibenzocarbazole losing a molecule of hydrogen upon being heated in the open air:



As homologs of tetralone-2 have now become readily accessible through the Cornforth-Robinson reduction of β-methoxynaphthalenes (12), this procedure makes possible the synthesis of homologs of 3,4,5,6-dibenzocarbazole, and this work is being continued.

Most of the new substances quoted above are now under biological investigation by Professor Lacassagne for potential carcinogenic and growth-inhibitory properties.

EXPERIMENTAL[3]

Preparation of intermediates. α- and β-*Naphthylhydrazine hydrochlorides* used in these experiments were prepared by reduction of α- and β-naphthyldiazonium chlorides with stannous chloride, according to the literature (yield 80–85%).

Tetralone-1 was conveniently obtained in 95% yield from γ-phenylbutyryl chloride by cyclization with aluminum chloride in benzene medium at 0°, and this procedure was found superior to the catalyzed air-oxidation of tetralin.

7-Methyltetralone-1 (13) was similarly prepared in 90% yield by cyclization of γ-*p*-tolylbutyric chloride; the intermediary γ-*p*-tolylbutyric acid was obtained either by Clemmensen reduction of γ-*p*-toluoylpropionic acid, according to Martin (14), or better, in large scale preparations and with 40% over-all yield, by a malonic ester synthesis starting from β-*p*-tolylethanol *via* β-*p*-tolylethyl bromide.

7-ter-Butyltetralone-1 was obtained from *ter*-butylbenzene according to Buu-Hoï and Cagniant (15).

7-Methoxytetralone-1 (16) was prepared by cyclization of γ-*p*-anisylbutyryl chloride, also in benzene solution at −5° to 0°. In this case too, the malonic ester synthesis of γ-*p*-anisylbutyric acid, starting from β-*p*-anisylethyl bromide, is preferable in large scale operations to the Clemmensen-Martin reduction of γ-*p*-anisoylpropionic acid (14).

7-Nitrotetralone-1 was obtained in excellent yield by nitration of tetralone-1 with fuming nitric acid (d = 1.49), according to von Braun's procedure (17).

Tetralone-2 was prepared from neroline as indicated in the literature (18); a considerable dropping off in the yield was noticeable when more than 25 to 30 g. of neroline was reduced at a time. It may be mentioned that the blue-colored substance which arises when tetralone-2 comes into contact with alkaline reagents is probably an indigoid dye resulting from the oxydative duplication of the molecule.

The *reagent* for the cyclization of the hydrazones was made by saturating pure acetic acid with dry hydrochloric acid.

3,4-Dihydro-1,2,7,8-dibenzocarbazole (VI; R = H). A mixture of 2.6 g. of tetralone-1, 4 g. of α-naphthylhydrazine hydrochloride, and 3 g. of sodium acetate, was refluxed with 50 ml. of ethanol for two hours. After cooling, an excess of water was added; the precipitate of the crude naphthylhydrazone was collected by suction, washed with water, and dissolved in 20 ml. of the cyclization reagent. After five minutes of heating on a water-bath, the mixture was poured into water, and the precipitate was washed thoroughly with water, dried, and crystallized from mixture of benzene and ligroïn. Almost colorless prisms melting at 178°, easily soluble in benzene, and giving a dark brown coloration with an alcoholic solution of picric acid were obtained. The yield was 2.5 g.

Anal. Calc'd for $C_{20}H_{15}N$: N, 5.2. Found: N, 5.3.

1,2,7,8-Dibenzocarbazole. A mixture of 1.2 g. of the foregoing dihydro compound, 1.7 g. of chloranil, and 30 ml. of dry xylene was refluxed for two hours. After cooling, the tetrachlorohydroquinone was filtered off by suction and washed with some ml. of xylene; the filtrate was shaken with a 10% aqueous solution of sodium hydroxide and then with water, and dried over calcium chloride. After the evaporation of xylene in a vacuum, the residue obtained was recrystallized twice from benzene, giving pale yellowish needles (1 g.) melting at 212°, and dissolving in sulfuric acid with a brown-red halochromic coloration. Nietzski and Goll (5) report the melting point as 216°.

2'-Nitro-3,4-dihydro-1,2,7,8-dibenzocarbazole (VI; R = NO_2). Reaction between 3.5 g. of 7-nitrotetralone-1, 5.5 g. of α-naphthylhydrazine hydrochloride, and 4.2 g. of sodium acetate in 50 ml. of alcohol gave a crude naphthylhydrazone which was cyclized as in the preceding case. Crystallization from xylene of the substance thus obtained gave fine, bright red needles melting at 270°. The yield was 2 g. Prolonged heating above the melting point transformed this substance into the following one.

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[3] All melting points are uncorrected, and were taken with a Maquenne-block.

Anal. Calc'd for $C_{20}H_{14}N_2O_2$: N, 8.9. Found: N, 8.6.

2'-Nitro-1,2,7,8-dibenzocarbazole (I; R = NO_2). Dehydrogenation of 1.7 g. of the preceding compound with 1.5 g. of chloranil in 40 ml. of xylene for two hours, followed by the usual treatment, gave a substance (1.5 g.) which crystallized from xylene in fine, shiny, deep red needles melting at 358°, almost insoluble in alcohol, easily soluble in pyridine.

Anal. Calc'd for $C_{20}H_{12}N_2O_2$: N, 8.9. Found: N, 8.6.

2'-Methoxy-3,4-dihydro-1,2,7,8-dibenzocarbazole (VI; R = OCH_3). This substance was obtained with a yield of 3 g. from 3 g. of 7-methoxytetralone-1, 5 g. of α-naphthylhydrazine hydrochloride, and 3 g. of sodium acetate, following the usual procedure. It crystallized from ligroïn in fine, pale yellowish needles melting at 173–174°, very soluble in benzene.

Anal. Calc'd for $C_{21}H_{17}NO$: N, 4.7. Found: N, 4.6.

2'-Methoxy-1,2,7,8-dibenzocarbazole (I; R = OCH_3). Dehydrogenation of 2 g. of the dihydro compound with 3 g. of chloranil in 40 ml. of xylene for two hours gave 1.5 g. of a substance separating from benzene in pale yellowish needles melting at 187°, giving a brown-red coloration with sulfuric acid.

Anal. Calc'd for $C_{21}H_{15}NO$: N, 4.7. Found: N, 4.7.

3,4-Dihydro-1,2,5,6-dibenzocarbazole (VIII; R = H). Two and six-tenths g. of tetralone-1, treated with 4 g. of β-naphthylhydrazine and 3 g. of sodium acetate, gave a naphthylhydrazone which was cyclized as usual; the compound obtained (2.5 g.) crystallized from benzene in almost colorless prisms melting at 197°.

Anal. Calc'd for $C_{20}H_{15}N$: N, 5.2. Found: N, 5.0.

1,2,5,6-Dibenzocarbazole. One and one-tenth g. of the foregoing compound treated with 1.5 g. of chloranil gave an almost quantitative yield of the dehydrogenated product, which crystallized from benzene in pale yellowish needles melting at 237–238°. The literature (4, 8) indicates 231° as the melting point.

2'-Nitro-1,2,5,6-dibenzocarbazole (II; R = NO_2). A mixture of 3.5 g. of 7-nitrotetralone-1, 5.5 g. of β-naphthylhydrazine hydrochloride, and 4.2 g. of sodium acetate was refluxed for two hours with 100 ml. of ethanol. After cyclization of the naphthylhydrazone in the usual way, a red substance was obtained, which was practically insoluble in the ordinary solvents. After crystallization from nitrobenzene, shiny deep red prisms were obtained, which melted at 365°; the yield was 3.5 g. This substance was recovered unchanged after treatment with chloranil.

Anal. Calc'd for $C_{20}H_{12}N_2O_2$: N, 8.9. Found: N, 8.7.

2'-Methyl-3,4-dihydro-1,2,5,6-dibenzocarbazole (VIII; R = CH_3). This substance was obtained with a yield of 5 g. from 3.2 g. of 7-methyltetralone-1, 5 g. of β-naphthylhydrazine, and 4.5 g. of sodium acetate. It separated from benzene in pale yellowish microcrystalline prisms melting at 228°, and giving a dark brown complex with picric acid.

Anal. Calc'd for $C_{21}H_{17}N$: N, 5.2. Found: N, 5.0.

2'-Methyl-1,2,5,6-dibenzocarbazole (II; R = CH_3). Dehydrogenation of 5 g. of the preceding substance with 7 g. of chloranil in 50 ml. of xylene gave an almost quantitative yield of a compound separating from xylene in pale yellowish microcrystalline prisms melting at 285–286°.

Anal. Calc'd for $C_{21}H_{15}N$: N, 5.2. Found: N, 4.9.

2'-ter-Butyl-3,4-dihydro-1,2,5,6-dibenzocarbazole. From 1.5 g. of 7-*ter*-butyltetralone-1, 3 g. of β-naphthylhydrazine hydrochloride, and 2.6 g. of sodium acetate, a hydrazone was obtained which, on cyclization, gave a substance crystallizing from ligroïn in almost colorless needles melting at 169–170° and giving a dark brown complex with picric acid. The yield was 1 g.

Anal. Calc'd for $C_{24}H_{21}N$: N, 4.3. Found: N, 4.0.

2'-ter-Butyl-1,2,5,6-dibenzocarbazole. This substance, obtained from 1 g. of the preceding dihydro compound and 1.5 g. of chloranil with an almost quantitative yield, crystallized from benzene in pale yellowish needles melting at 226°.

Anal. Calc'd for $C_{24}H_{19}N$: N, 4.3. Found: N, 4.0.

2'-Methoxy-3,4-dihydro-1,2,5,6-dibenzocarbazole. Three grams of 7-methoxytetralone-1,

5 g. of β-naphthylhydrazine hydrochloride, and 3 g. of sodium acetate, yielded 4.5 g. of this substance, which separated from benzene in microcrystalline yellowish prisms melting at 200°.

Anal. Calc'd for $C_{21}H_{17}NO$: N, 4.7. Found: N, 4.5.

2'-Methoxy-1,2,5,6-dibenzocarbazole (II; R = OCH_3). Four and one-half g. of the foregoing compound, treated with 5 g. of chloranil, gave 4 g. of the dehydrogenated product, which crystallized from xylene in fine yellowish prisms melting at 258°. Brown-red coloration with sulfuric acid.

Anal. Calc'd for $C_{21}H_{15}NO$: N, 4.7. Found: N, 4.5.

3,4,5,6-Dibenzocarbazole (III). A mixture of 1.5 g. of tetralone-2, 2.5 g. of β-naphthylhydrazine hydrochloride, and 2 g. of sodium acetate was refluxed in 40 ml. of ethanol for one hour, and the crude naphthylhydrazone indolized as usual. The cyclization product (1 g.) was either distilled or heated with chloranil (1.4 g.) in xylene solution for one hour, and the mixture worked up as usual. One gram of 3,4,5,6-dibenzocarbazole was obtained, which crystallized from a mixture of benzene and ligroïn in fine yellowish prisms melting at 154°. The literature (4, 8) gives 155°.

SUMMARY

1. A convenient method is described for the preparation of the three carcinogenic bis-angular dibenzocarbazoles.

2. The synthesis is reported of a number of functional derivatives and homologs of 1,2,7,8- and 1,2,5,6,-dibenzocarbazole, desired for biological experimentation.

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