Electrophilic Substitution Reactions in 4*H*-Benzo[*d*,*e*,*f*]carbazole

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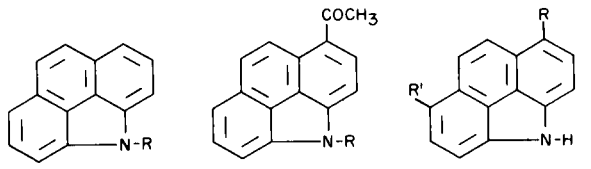
The behavior of 4*H*-benzo[*d*,*e*,*f*]carbazole and its *N*-acetyl derivative in various electrophilic substitution reactions (e.g. nitration, nitrosation, bromination, Friedel-Crafts acylations) has been investigated, and a number of new derivatives of this heterocycle (some of which are to be tested as potential carcinogens and enzyme-inducers) have been synthesized.

4*H*-Benzo[*d*,*e*,*f*]carbazole (I), a constituent of coal tar hitherto rarely investigated (1), combines in its molecular framework a phenanthrene structure and a carbazole nucleus, both of which are known to impart potential carcinogenic (2) and enzyme-inducing (3) properties to their derivatives. Although 4*H*-benzo[*d*,*e*,*f*]carbazole itself is devoid of tumor-producing activity (4), it is possible that some compounds derived from it (in particular the amino-derivatives) might prove to be carcinogenic and for this reason we undertook an investigation of the behavior of I in various electrophilic reactions.

Prior to our work, few data were available concerning the reactivity of I. Zander and Franke (5) investigated its Friedel-Crafts *o*-toluoylation and thus prepared a monoketone and a diketone, which were considered to be the 1- and 1,7-derivatives, respectively (although the positions 2 and 6 cannot be ruled out by their results). Earlier, Kruber and Grigoleit (1) had briefly examined the acetylation of I by acetic anhydride in the presence of sulfuric acid and found it to give 4-acetyl-4*H*-benzo[*d*,*e*,*f*]-carbazole (II). We found that this last compound and other similar *N*-acyl compounds could be prepared in good yield only when the catalyst was omitted (another acceptable procedure consists of using acetic acid in the presence of zinc chloride); Kruber and Grigoleit's method generally resulted in the formation of substantial amounts of 1,4-diacetyl-4*H*-benzo[*d*,*e*,*f*]carbazole (IV), which was readily converted by Wolff-Kishner reduction [following Huang-Minlon's technique (6)] into 1-ethyl-4*H*-benzo[*d*,*e*,*f*]-carbazole (VI) either directly, or *via* 1-acetyl-4*H*-benzo-[*d*,*e*,*f*]carbazole (V). Aluminum chloride-catalyzed Friedel-Crafts acylations effected in methylene chloride medium resulted in disubstitution, 1,7-diacetyl- (VII) and 1,7-dipropionyl-4*H*-benzo[*d*,*e*,*f*]carbazole (VIII) being obtained, along with very small amounts of corresponding isomeric diketones of unknown structure. Again, Wolff-Kishner reduction of compound VII readily afforded 1,7-diethyl-4*H*-benzo[*d*,*e*,*f*]carbazole (IX). Proof for the structures of ketones VII (and hence of compound IX) and VIII was provided by their nuclear magnetic resonance spectra which showed complete symmetry and unequivocally attributable peaks (Fig. 1). The structure of ketone V was proven by its Friedel-Crafts acetylation to the diketone VII.



I R = H
II R = $COCH_3$
III R = NO

IV R = $COCH_3$
V R = H

VI R = C_2H_5; R' = H
VII R = R' = $COCH_3$
VIII R = R' = COC_2H_5
IX R = R' = C_2H_5

4*H*-Benzo[*d*,*e*,*f*]carbazole was too reactive for direct nitration, but its *N*-acetyl derivative could be nitrated to a product which, on deacetylation and subsequent reduction, afforded a monoamine. This was certainly the 1-derivative (X), in view both of the sites of substitution in Friedel-Crafts reactions, and of Clemo and Felton's remarks on carbazole *para*-quinanoid states (for instance XI, in which privileged electrophilic substitution takes place in the positions *para* to the heterocyclic nitrogen atom (7).

The *N*-nitroso- derivative of 4*H*-benzo[*d*,*e*,*f*]carbazole was readily prepared by means of potassium nitrite and acetic acid, and its structure ascertained by reconversion to I with hydrazine hydrate and Raney nickel.

Direct reaction of I with bromine was shown by Zander and Franks (5) to give a tetrasubstitution-product. Controlled bromination could, however, be achieved by

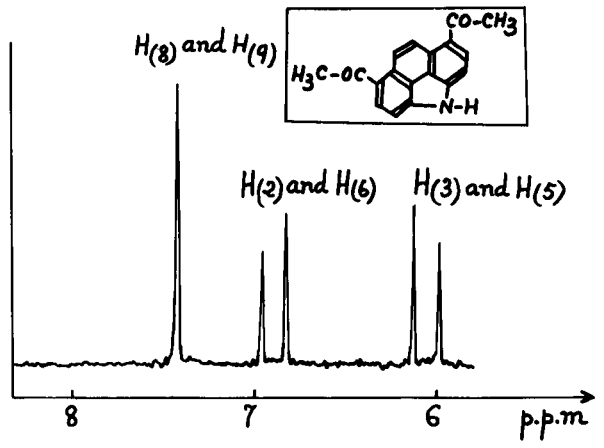
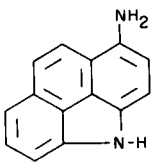


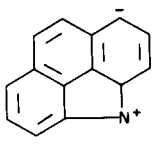
Figure 1

the action of *N*-bromosuccinimide on the *N*-acetyl derivative (II), carbazoles being known to react with *N*-bromoimides more mildly than with the free halogen (8); and by converting the *N*-acetyl derivative (II) into the free carbazole (I). In these conditions, a monobromo compound could be easily obtained; its *N*-deacetylation furnished a mono-4*H*-benzo[*d*,*e*,*f*]carbazole which, in view both of the *para* orientation constantly observed in the halogenation of carbazole (8), and of Clemo and Felton's rule (7), must be 1-bromo-4*H*-benzo[*d*,*e*,*f*]carbazole (XII). In this reaction, some disubstitution was observed, and a pure compound, considered for similar reasons as 1,7-dibromo-4*H*-benzo[*d*,*e*,*f*]carbazole (XIII), could be isolated after *N*-deacetylation.

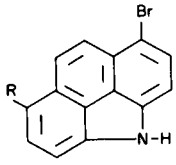
4*H*-Benzo[*d*,*e*,*f*]carbazole itself failed to give a pure *ortho*-quinone on oxidation with sodium dichromate in acetic acid, but under the same reaction conditions, its *N*-acetyl derivative afforded small amounts of 4-acetyl-4*H*-benzo[*d*,*e*,*f*]carbazole-8,9-quinone (XIV).



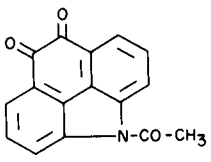
X



XI



XII R = H
XIII R = Br



XIV

EXPERIMENTAL

4-Acetyl-4*H*-benzo[*d*,*e*,*f*]carbazole (II).

Method 1.

A solution of the carbazole (I) (19.1 g.) in acetic anhydride (40 ml.) was heated under reflux for 20 hours, and then kept at room temperature for 12 hours. The precipitate was collected, washed thoroughly with ethanol, and dried, giving compound II in 87% yield, as long colorless needles, m.p. 178-179°.

Anal. Calcd. for $C_{16}H_{11}NO$: C, 82.4; H, 4.8; N, 6.0. Found: C, 82.3; H, 4.7; N, 5.8.

Method 2.

A solution of the carbazole I (1.9 g.) in acetic acid (5 ml.) was heated on a water-bath for 1.5 hours with anhydrous zinc chloride (1 g.), and the product was worked up in the usual way giving compound II in 55% yield.

Other Acetylations of I.

A. 4-Propionyl-4*H*-benzo[*d*,*e*,*f*]carbazole.

This compound was prepared by Method 1 with propionic anhydride and was crystallized from ethanol giving long silky colorless needles, m.p. 129-130°, yield 62%.

Anal. Calcd. for $C_{17}H_{13}NO$: C, 82.6; H, 5.3; N, 5.7. Found: C, 82.4; H, 5.2; N, 5.6.

B. 4-Butyryl-4*H*-benzo[*d*,*e*,*f*]carbazole.

This compound was prepared by Method 1 with butyryl chloride and was crystallized from ethanol to give long colorless needles, m.p. 140-141°, yield 60%.

Anal. Calcd. for $C_{18}H_{15}NO$: C, 82.8; H, 6.0; N, 5.4. Found: C, 82.7; H, 5.8; N, 5.4.

4-Acetyl-4*H*-benzo[*d*,*e*,*f*]carbazole-8,9-quinone (XIV).

A suspension of 1 g. of compound II in a solution of 2 g. of sodium dichromate in 25 ml. of acetic acid was heated under reflux for 30 hours, and 200 ml. of water was added on cooling. The brown precipitate was repeatedly crystallized from acetic acid, and the red product obtained was further purified by vacuum-sublimation to give compound XIV as red, microscopic needles (0.05 g.), m.p. 400°.

Anal. Calcd. for $C_{16}H_9NO_3$: C, 73.0; H, 3.5; N, 5.3. Found: C, 73.4; H, 3.5; N, 5.1.

Sulfuric Acid-catalyzed Acetylation of I.

A solution of 3.8 g. of carbazole I in 10 ml. of acetic anhydride was treated with 3 drops of sulfuric acid and the mixture was gently heated under reflux for 1 hour. After cooling and dilution with 300 ml. of water, the oil which formed was taken up in hot ethanol, the ethanolic solution was concentrated, and the solid which formed on cooling was crystallized first from acetone, then from ethanol, to give 1,4-diacetyl-4*H*-benzo[*d*,*e*,*f*]carbazole (IV) as pale yellow leaflets, m.p. 173-174°, in 35% yield. The solution in concentrated sulfuric acid was orange-red.

Anal. Calcd. for $C_{18}H_{13}NO_2$: C, 78.5; H, 4.8; N, 5.1. Found: C, 78.5; H, 4.8; N, 4.9.

1-Acetyl-4*H*-benzo[*d*,*e*,*f*]carbazole (V).

A solution of 0.7 g. of compound IV in 150 ml. of ethanol was treated with 1 g. of potassium hydroxide, and the mixture was heated under reflux for 2 hours. After partial evaporation of the solvent and addition of water to the residue, the precipitate obtained was crystallized twice from ethanol, giving 0.5 g. of short

yellow prisms, m.p. 233°. The solution in sulfuric acid was orange-red.

Anal. Calcd. for $C_{16}H_{11}NO$: C, 82.4; H, 4.8; N, 5.8. Found: C, 82.1; H, 4.8; N, 5.8.

1-Ethyl-4*H*-benzo[*d*,*e*,*f*]carbazole (VI).

A solution of 0.3 g. of the foregoing ketone and 3 ml. of 95% hydrazine hydrate in 30 ml. of diethylene glycol was heated for 2 minutes at 100°. After addition of 0.6 g. of potassium hydroxide, the mixture was heated under reflux for 40 hours. On cooling, 250 ml. of water was added, and the precipitate was collected, washed with water, and recrystallized twice from hexane, giving compound VI as colorless needles, m.p. 139-140°, in 80% yield. The solution in sulfuric acid was yellow.

Anal. Calcd. for $C_{16}H_{13}N$: C, 87.6; H, 6.0. Found: C, 87.4; H, 5.9.

The same compound was obtained by a similar treatment of the diacetyl compound (IV).

Aluminum Chloride-catalyzed Acetylation of I.

To a solution of carbazole I (3.6 g.) in 50 ml. of methylene chloride was added a complex made from 6.2 g. of aluminum chloride and 3.6 g. of acetyl chloride in 50 ml. of methylene chloride over a period of 30 minutes, with stirring. After a further addition of 200 ml. of solvent, the dark red mixture obtained was heated under reflux for 10 hours, then allowed to stand for 10 more hours at room temperature. After decomposition with aqueous hydrochloric acid, the precipitate which formed was crystallized from acetic acid, to give 1,7-diacetyl-4*H*-benzo[*d*,*e*,*f*]-carbazole (VII) as pale yellow, sublimable prisms, m.p. 305°. Solutions of VII in sulfuric acid were orange-red. The same compound was obtained by replacing the carbazole (I) by ketone V.

Anal. Calcd. for $C_{18}H_{13}NO_2$: C, 78.5; H, 4.7; N, 5.1. Found: C, 78.2; H, 4.7; N, 4.9.

The methylene chloride layer contained, in addition to the foregoing compound, an isomeric *x*,*y*-diacetyl-4*H*-benzo[*d*,*e*,*f*]-carbazole, which when crystallized from acetic acid, then from benzene, and finally from acetone, gave pale yellow, sublimable needles (0.25 g.), m.p. 263-265°.

Anal. Calcd. for $C_{18}H_{13}NO_2$: C, 78.5; H, 4.7; N, 5.1. Found: C, 78.1; H, 4.7; N, 5.2.

Aluminum Chloride-catalyzed Propionylation of I.

The reaction of propionyl chloride with carbazole I, effected in methylene chloride as above, afforded in 20% yield, 1,7-dipropionyl-4*H*-benzo[*d*,*e*,*f*]carbazole (VIII), which was crystallized from acetic acid and then from methyl ethyl ketone, to give lemon yellow prisms, m.p. 288°. A solution of the product in sulfuric acid was orange.

Anal. Calcd. for $C_{20}H_{17}NO_2$: C, 79.2; H, 5.7; N, 4.6. Found: C, 79.3; H, 5.6; N, 4.4.

Small amounts of an isomeric *x*,*y*-dipropionyl-4*H*-benzo[*d*,*e*,*f*]-carbazole, recovered from the methylene chloride layer, were recrystallized from ethanol to give yellow leaflets, m.p. 219°. The solutions in sulfuric acid were red.

Anal. Calcd. for $C_{20}H_{17}NO_2$: C, 79.2; H, 5.7; N, 4.6. Found: C, 79.0; H, 5.7; N, 4.3.

1,7-Diethyl-4*H*-benzo[*d*,*e*,*f*]carbazole (IX).

A solution of 0.4 g. of diketone VII in 25 ml. of diethylene glycol when heated for a few minutes at 100° with 4 ml. of hydrazine hydrate, formed the corresponding hydrazone. Potassium hydroxide (0.4 g.) was then added, and the mixture was heated under reflux for 17 hours. After the usual treatment, 1,7-diethyl-4*H*-benzo[*d*,*e*,*f*]carbazole (IX) was obtained in 70% yield. Crystallization from ethanol gave colorless needles, m.p. 196°. There was no coloration in sulfuric acid.

Anal. Calcd. for $C_{18}H_{17}N$: C, 87.4; H, 6.9; N, 5.7. Found: C, 87.3; H, 6.7; N, 5.7.

An isomeric diethyl compound, similarly prepared from the diacetyl-4*H*-benzo[*d*,*e*,*f*]carbazole, m.p. 264-264°, crystallized from ethanol as colorless needles, m.p. 123°.

Anal. Calcd. for $C_{18}H_{17}N$: C, 87.4; H, 6.9; N, 5.7. Found: C, 87.3; H, 7.1; N, 5.6.

4-Nitroso-4*H*-benzo[*d*,*e*,*f*]carbazole (III).

A solution of 5.7 g. of carbazole I in 200 ml. of acetic acid was treated at 18° with 2.2 g. of sodium nitrite with stirring. After standing for 30 minutes at room temperature, water was added, and the precipitate was collected and crystallized several times from ethanol to give the nitroso compound III as long, golden-yellow needles (3.6 g.), m.p. 190-191°. The position of the nitroso group was determined by treatment with Raney nickel in boiling ethanol, whereby 4*H*-benzo[*d*,*e*,*f*]carbazole was recovered.

Anal. Calcd. for $C_{14}H_8N_2O$: N, 12.7. Found: N, 12.4.

Nitration of 4-Acetyl-4*H*-benzo[*d*,*e*,*f*]carbazole.

Attempts to nitrate 4*H*-benzo[*d*,*e*,*f*]carbazole with nitric acid were unsuccessful and led only to dark-colored intractable resins. A solution of its *N*-acetyl derivative (2.33 g.) in 50 ml. of acetic acid was treated dropwise with 1 ml. of nitric acid (d = 1.49), with stirring. After 6 hours, the precipitate which formed on dilution with water was collected, washed thoroughly with water, and recrystallized repeatedly from acetic acid, to give 4-acetyl-1-nitro-4*H*-benzo[*d*,*e*,*f*]carbazole as pale yellow prisms (1 g.), m.p. 254°. The coloration in sulfuric acid was brown.

Anal. Calcd. for $C_{16}H_{10}N_2O_3$: C, 69.1; H, 3.6; N, 10.1. Found: C, 69.0; H, 3.7; N, 10.3.

1-Nitro-4*H*-benzo[*d*,*e*,*f*]carbazole.

Deacetylation of the foregoing compound (3.5 g.) in 300 ml. of diethylene glycol was achieved by heating for 30 minutes at 130° with 1.5 g. of sodium hydroxide. 1-Nitro-4*H*-benzo[*d*,*e*,*f*]-carbazole, obtained as a precipitate on dilution with water, was collected and recrystallized from methyl ethyl ketone, to give 1.5 g. of brick red, sublimable needles, m.p. 288°.

Anal. Calcd. for $C_{14}H_8N_2O_2$: C, 71.2; H, 3.4; N, 11.9. Found: C, 71.0; H, 3.4; N, 11.7.

1-Amino-4*H*-benzo[*d*,*e*,*f*]carbazole (X).

A suspension of 0.7 g. of the foregoing nitro compound in 80 ml. of ethanol was heated under reflux for 2 hours with 1 ml. of hydrazine hydrate and 0.5 g. of Raney nickel. After cooling, the catalyst was filtered off, and the filtrate was concentrated. The precipitate obtained on cooling was recrystallized from heptane, to give the amine (X) as pale yellow leaflets (0.3 g.), m.p. 219-220°, which darkened rapidly on exposure to air and light.

Anal. Calcd. for $C_{14}H_{10}N_2$: C, 81.5; H, 5.0; N, 13.6. Found: C, 81.5; H, 5.0; N, 13.6.

Bromination of 4-Acetyl-4*H*-benzo[*d*,*e*,*f*]carbazole.

To a solution of 4.6 g. of compound II in 50 ml. of boiling, dry carbon tetrachloride, 4.3 g. of *N*-bromosuccinimide was added in small portions, and the mixture was heated under reflux for 50 hours. The succinimide was then filtered off, the solvent was evaporated, and the residue was washed thoroughly with water. Recrystallization from acetone afforded a 40% yield of 4-acetyl-

1-bromo-4*H*-benzo[*d,e,f*]carbazole as fine colorless prisms, m.p. 175-176°.

Anal. Calcd. for $C_{16}H_{10}BrNO$: C, 61.4; H, 3.5; N, 4.5; Br, 25.5. Found: C, 61.2; H, 3.4; N, 4.5; Br, 25.7.

1-Bromo-4*H*-benzo[*d,e,f*]carbazole (XII).

A solution of 0.9 g. of the foregoing *N*-acetyl derivative in 80 ml. of acetone was treated with a solution of 2 g. of sodium hydroxide in 10 ml. of water, and the mixture was heated under reflux for 5 hours. After cooling, the acetone was distilled off, and the residue was washed with water and recrystallized several times from petroleum ether, to give compound XII as shiny colorless leaflets, m.p. 190-191°, yield 0.5 g. The solutions in sulfuric acid were lemon-yellow.

Anal. Calcd. for $C_{14}H_8BrN$: C, 62.2; H, 3.0; N, 5.2; Br, 29.6. Found: C, 62.2; H, 3.1; N, 5.0; Br, 29.6.

1,7-Dibromo-4*H*-benzo[*d,e,f*]carbazole (XIII).

As a by-product of the monobromination of II, small amounts of a dibromo-**derivative were** obtained and upon crystallization from benzene **formed** prisms, m.p. 248-249°. On deacetylation with sodium hydroxide in acetone, this product gave 1,7-dibromo-4*H*-benzo[*d,e,f*]carbazole (XIII), which crystallized from ethanol as shiny colorless leaflets, m.p. 264-265°.

Anal. Calcd. for $C_{14}H_7Br_2N$: Br, 45.8. Found: Br, 46.1.

Bromination of I.

To a solution of 1.9 g. of I in 130 ml. of boiling carbon tetrachloride, 2.15 g. of *N*-bromosuccinimide was added in small portions, and the mixture was heated under reflux for 30 minutes. The crude bromination product obtained after the usual treatment afforded, after several fractional recrystallizations, a portion (0.2 g.) soluble in pentane, which was identified as XII, and a less soluble portion which was identified as XIII.

N.M.R. Studies.

N.m.r. spectra were taken on a Varian A-60 apparatus; the solvent used was dimethylsulfoxide, with tetramethylsilane as internal reference. Figure 1 gives the aromatic portion of the spectrum of diketone VII (the six aliphatic protons appear as a single peak at 2.81 p.p.m.); it showed (a) a doublet (7.73 p.p.m.) corresponding to protons 3 and 5, with an *ortho*-coupling with protons 2 and 6 (J = 8 c.p.s.), (b) a doublet (8.56 p.p.m.) corresponding to protons 2 and 6, with an *ortho*-coupling (J = 8 c.p.s.), protons 2 and 6 being unshielded by the neighboring acetyl groups; (c) a singlet (9.08 p.p.m.) corresponding to protons 8 and 9 which are strongly unshielded by the acetyl groups located in *peri* position. The spectrum of the higher homolog (VIII) is almost identical to that of compound VII in its aromatic portion.

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