

Selective Photo-bromination in the Carbazole Series: A Study

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Selective radical bromination of 3-methylcarbazole on the methyl group would be difficult because of the free positions *ortho* and *para* to the imino group (1). The only known procedure for brominating a derivative of 3-methylcarbazole involves 1-methoxy-3-methylcarbazole with *N*-bromosuccinimide in the presence of benzoyl peroxide; however, the bromo derivative was hydrolyzed *in situ* to 1-methoxy-3-hydroxymethylcarbazole in less than 10% overall yield (2). Such low yields would be expected, upon considering the results of N. P. Buu-Hoi on nuclear substitution of the carbazole nucleus by *N*-bromosuccinimide under similar conditions (3).

Various 9-substituents which reduce the electron donating power of the heteroatom have been used to prepare 3-nitrocarbazole in good yield by the procedure of Ruff and Stein (7).

A group was desired that would deactivate the 3-methylcarbazole nucleus to nuclear substitution and allow selective bromination of the methyl group. In addition, the group must be put on and taken off with ease, be stable to hydrogen bromide, not induce side reactions, and be resistant to Friedel-Crafts reactions, since our final goal is to build up the side chain to obtain higher polynuclear derivatives of carbazole in the future.

The 9-nitroso blocking group was immediately eliminated because of its sensitivity to acid (8). The 9-alkyl substituents were eliminated on two accounts: they were not electron withdrawing enough to prevent bromination of the nucleus and removal of the 9-alkyl group required destructive conditions, 300° with sulfur (3,9). For example, attempted dealkylation of 9-ethyl-3-carbazolcarboxaldehyde and 9-ethyl-3-acetylcarbazole was accompanied by complete cleavage of the formyl group and almost complete (85%) cleavage of the acetyl group. The migratory habits of the 9-acyl groups to the carbazole nucleus in the presence of Lewis acids precluded their use as blocking groups (10). Finally, the presence of an additional nuclear methyl group on the 9-(*p*-toluenesulfonyl)-3-methylcarbazole prompted the rejection of the 9-(*p*-toluenesulfonyl) group.

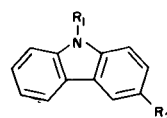
Carbon tetrachloride solutions of a series of *N*-substituted carbazoles and carbazole were allowed to stand

in pyrex cuvettes with bromine in the absence of light. The reactivity carbazole and 9-ethylcarbazole was high, bromination was complete within 15 seconds. Compounds 1 through 1d (Table) showed negligible halogenation after 0.5 hour.

After irradiation (high pressure mercury source) 9-benzoyl-3-methylcarbazole and 9-benzenesulfonyl-3-methylcarbazole had consumed all detectable bromine; whereas, the remaining 9-substituted carbazoles (Table) showed loss of bromine comparable to that observed in the dark reactions.

Photo-bromination of 9-benzenesulfonyl-3-methylcarbazole (1) on a preparative scale resulted in a reaction mixture which by nmr spectroscopy contained 80% of 9-benzenesulfonyl-3-bromomethylcarbazole (II), 10% of 9-benzenesulfonyl-3-dibromomethylcarbazole, and 10% of

TABLE I
Photobromination of



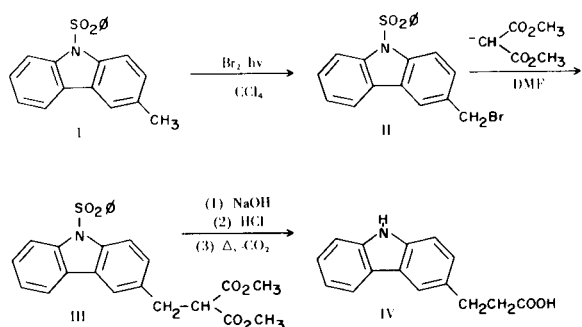
| Structure | R ₁ | R ₂ | Percent Bromine Consumed (a) | |
|-----------|------------------------------------|-------------------|------------------------------|-----------|
| | | | Dark (b) | Light (c) |
| I | φ-SO ₂ - | CH ₃ - | 1.0 | 100 |
| Ia | φ-CO- | CH ₃ - | 1.3 | 100 |
| Ib | φ-SO ₂ - | H- | 1.0 | 1.3 |
| Ic | φ-CO- | H- | 1.3 | 2.0 |
| Id | CH ₃ -CO- | H- | 1.0 | 1.3 |
| Ie | CH ₃ -CH ₂ - | H- | 100 | |
| If | H- | H- | 100 | |

(a) The reaction mixture, contained in a pyrex cuvette, was 0.024 *M* in the carbazole derivative and 0.021 *M* in bromine in carbon tetrachloride solvent. The bromine concentration was estimated spectrophotometrically (see experimental). The error was ±0.5% bromine. The reaction time was 0.5 hour. (b) The temperature was 26.0° ± 0.1°. (c) The temperature was 26.2° ± 0.2°. A water-cooled Osram Mercury-Cadmium spectral lamp was used.

starting material from which the major constituent was isolated in high yield (70%).

Formation of 3-bromo-9-(*p*-toluenesulfonyl)carbazole via nuclear bromination of 9-(*p*-toluenesulfonyl)carbazole was observed by D. H. Peacock under typical ionic conditions (acetic acid, 60-70°, longer reaction time) in contrast to our specific radical conditions (carbon tetrachloride, 20° (4)).

To exemplify the versatility of this synthetic intermediate, 9-benzenesulfonyl-3-bromomethylcarbazole (II) was reacted with the sodium salt of dimethyl malonate. The resulting dimethyl 9-benzenesulfonyl-3-carbazolylmethylmalonate (III) without further purification was hydrolyzed, acidified, thermally decarboxylated and recrystallized from xylene to give colorless plates of 3-(3-carbazolyl)propionic acid (IV) (58% from II). The 5,6,7,8-tetrahydro derivative has been prepared by a difficult and circuitous synthesis (11).



EXPERIMENTAL.

Carbazole (m.p. 245.7°, lit. m.p. 245.6°) (12), 3-methylcarbazole (m.p. 204.0°, lit. m.p. 203°) (13), 9-ethylcarbazole (m.p. 68.5°, lit. m.p. 70°) (14), 9-acetylcarbazole (m.p. 76.0°, lit. m.p. 75°) (15), and 9-benzoylcarbazole (m.p. 98.0°, lit. m.p. 98°) (16) were prepared according to published procedure. All other reagents used were of the highest commercial purity available.

9-Benzenesulfonylcarbazole.

In a dry system under nitrogen, a solution of 12.5 g. (0.075 mole) of carbazole and 8.8 g. (0.08 mole) of potassium *t*-butoxide in 100 ml. of *N,N*-dimethylformamide (dried over calcium hydride) was distilled until *t*-butyl alcohol was no longer collected. The residue was cooled to 10° with rapid stirring to give a suspension of the potassium derivative which was treated with 14 g. (0.08 mole) benzenesulfonyl chloride and allowed to stand at 25° with stirring for 2 hours. After precipitation with 400 ml. of water, the crude product was removed and recrystallized from toluene to give prisms, m.p. 132°, 19.6 g. (84% yield) (dried *in vacuo* at 80°); nmr (deuteriochloroform): aromatic multiplets centered at 7.28, 7.70, 8.22.

Anal. Calcd. for $\text{C}_{18}\text{H}_{13}\text{NSO}_2$: C, 70.36; H, 4.23; N, 4.56; S, 10.42. Found: C, 70.45; H, 4.31; N, 4.42; S, 10.58.

9-Benzenesulfonyl-3-methylcarbazole.

The above procedure applied to the synthesis of 9-benzenesulfonylcarbazole was followed exactly using 13.5 g. (0.075 mole)

of 3-methylcarbazole in place of carbazole. The large prisms amounted to 21 g. (81% yield), m.p. 147°; nmr (deuteriochloroform): 2.32 (s, 3H, CH_3), aromatic multiplets centered at 7.20, 7.58, 8.18 (12H).

Anal. Calcd. for $\text{C}_{19}\text{H}_{15}\text{NSO}_2$: C, 71.03; H, 4.67; N, 4.36; S, 9.97. Found: C, 71.17; H, 4.75; N, 4.30; S, 9.88.

9-Benzoyl-3-methylcarbazole.

The procedure applied to the synthesis of 9-benzenesulfonyl-3-methylcarbazole was followed except that 11.2 g. (0.08 mole) of benzoyl chloride was used. The colorless prisms weighed 19.5 g. (85% yield), m.p. 116°; nmr (deuteriochloroform): 2.48 (s, 3H, CH_3), aromatic multiplets centered at 7.25, 7.62, 7.95 (12H).

Anal. Calcd. for $\text{C}_{20}\text{H}_{15}\text{NO}$: C, 84.21; H, 5.26; N, 4.91. Found: C, 84.06; H, 5.31; N, 4.98.

9-Benzenesulfonyl-3-bromomethylcarbazole.

A stirred solution of 12.8 g. (0.04 mole) 9-benzenesulfonyl-3-methylcarbazole in 800 ml. of carbon tetrachloride (distilled from phosphorus pentoxide) was kept at 20° by external cooling and irradiated with a water cooled (pyrex water jacket) 200 watt Hanovia 654A-36 high pressure mercury lamp while a solution of 6.4 g. (0.04 mole) of bromine in 100 ml. of dry carbon tetrachloride was added in 1 ml. portions at such a rate that the red coloration of the reaction mixture is lost between additions. The resulting mixture (the nmr spectrum of this reaction mixture revealed the presence of approximately 80% of the desired bromomethyl derivative (CH_2Br singlet at 4.62), 10% of the dibromomethyl derivative (CHBr_2 singlet at 6.79), and 10% of the unreacted starting material (CH_3 singlet at 2.37) was evaporated under reduced pressure to remove the solvent and the residue crystallized from toluene-hexane after charcoal treatment in toluene. The yield of colorless prisms was 11.2 g. (70% yield), m.p. 144°; nmr (deuteriochloroform): 4.62 (s, 2H, CH_2Br) and aromatic multiplets centered at 7.32, 7.80, 8.22 (12H); ir potassium bromide): 1355 cm^{-1} and 1160 cm^{-1} (broad) (SO_2).

Anal. Calcd. for $\text{C}_{19}\text{H}_{14}\text{O}_2\text{BrNS}$: C, 57.0; H, 3.5; N, 3.5; Br, 19.97; S, 8.03. Found: C, 57.10; H, 3.58; N, 3.41; Br, 20.33; S, 7.94.

3-(3-Carbazolyl)propionic Acid.

Methanol was distilled from a mixture of 7.9 g. (0.06 mole) dimethyl malonate and 3.2 g. (0.06 mole) of sodium methoxide in 50 ml. of *N,N*-dimethylformamide (dried over calcium hydride). On cooling to 5°, 8.0 g. (0.02 mole) of 9-benzenesulfonyl-3-bromomethylcarbazole was added. After standing 8 hours at 25°, the mixture was poured into 500 ml. of water containing 20 ml. of concentrated hydrochloric acid. The resulting mixture was extracted with four 100 ml. portions of methylene chloride. The combined extracts were dried over anhydrous magnesium sulfate and the solvent removed *in vacuo*. The residue was dissolved in 50 ml. of methanol, poured into 500 ml. of 10% sodium hydroxide solution and refluxed for 48 hours. The reaction mixture was cooled to 85°, made strongly acid with concentrated hydrochloric acid and the precipitated product removed. The air dried solid was refluxed for 48 hours in 200 ml. of xylene, treated with decolorizing carbon, and cooled to 0°. The product crystallized as colorless plates, m.p. 224°, with darkening, 2.8 g. (58% yield); nmr (deuterioacetone): 2.72 (t, 2H, $\text{CH}_2\text{CH}_2\text{COOH}$); 3.10 (t, 2H, $\text{CH}_2\text{CH}_2\text{COOH}$), 5.30 (s, 1H, COOH), 10.12 (s, 1H, NH); resonances at 5.30 and 10.12 showed rapid exchange for deuterium with deuterium oxide; aromatic multiplets centered at 7.30, 8.05 (7H); ir (potassium bromide): 1700 cm^{-1} (C=O), 3050 cm^{-1} (OH), and 3430 cm^{-1} (NH).

Anal. Calcd. for $C_{15}H_{13}O_2N$: C, 75.31; H, 5.44; N, 5.86. Found: C, 75.20; H, 5.54; N, 5.99.

Bromination of *n*-Substituted Carbazoles in the Table.

The 9-substituted carbazole derivatives (1.6×10^{-4} mole) were dissolved in 10 ml. of carbon tetrachloride (distilled from phosphorus pentoxide) in pyrex cuvettes and bromine (7.0×10^{-5} mole) in 0.5 ml. of carbon tetrachloride was added to each at $26^\circ \pm 0.1^\circ$. After 0.5 hour dark reaction time, samples were collected. While percent bromine of the samples were recorded on a Cary 15 spectrophotometer, the pyrex cuvettes were circularly arranged 2 inches from an Osram Mercury-Cadmium spectral lamp equipped with a pyrex water jacket and irradiated for 0.5 hour at $26.2^\circ \pm 0.2^\circ$. Percent bromine of the irradiated solutions was recorded spectrophotometrically (Cary 15) at 413 nm and 450 nm.

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