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NITRATION IN THE CARBAZOLE SERIES

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Abstract—Nitration of 9-tosylcarbazole in acetic anhydride solution gives 1-nitro (28%), 2-nitro (19%) and 3-nitro (53%) derivatives. The mixture of the nitro compounds obtained from 9-acetylcarbazole contains 10%, 48% and 42% of the isomers, respectively. Under similar conditions 9-nitrosocarbazole shows a different isomer distribution: 34% of 1-nitro and 66% of 3-nitrocarbazole. Nitration of carbazole is a two step process involving formation and rearrangement of 9-nitrocarbazole. The hypothesis was supported by the results of 1,3,6,8-tetrachlorocarbazole nitration and oxidation of 9-nitrosocarbazole and rearrangement of 9-nitrocarbazole in the nitration conditions.

Nitration of carbazole with the stoichiometric amount of nitric acid in acetic acid solution gives 3-nitro and 1-nitrocarbazole in an approximately 7:3 ratio, contaminated with carbazole and its dinitro-derivatives. The rate of 9-alkylcarbazoles nitration is similar to that of carbazole but the isomers distribution is different; the 1-nitro derivative never exceeds 10% and is independent of the bulkiness of the alkyl group.[1]

We have assumed this difference to be the result of dissimilar reaction mechanisms: 9-alkylcarbazoles are substituted directly in aromatic rings while i-nitro and 3-nitrocarbazole are formed from 9-nitrocarbazole by an intramolecular rearrangement. The results of our experiment of 9-acylcarbazole nitration support this idea to some extent.

Nitration of 9-tosylcarbazole has been proposed for the preparation of 1-nitrocarbazole. The presence of the tosyl group has been supposed to prevent substitution at position 3.[2] Later it was shown that 9-tosylcarbazole could not be nitrated under the conditions described.[3] Nitration of 9-acetylcarbazole in boiling acetic acid solution was described long ago. The only product isolated in unspecified yield was 3-nitro-9-acetylcarbazole, identical with the product of acetylation of 3-nitrocarbazole.[4] 9-Nitrosocarbazole is an useful intermediate in 3-nitrocarbazole preparation. It forms 3-nitro-9-nitrosocarbazole when nitrated. The product crystallises readily from the reaction mixture and can be easily hydrolysed in alkaline solution.[5-7]

We have performed a series of nitrations of 9-tosyl, 9-acetyl and 9-nitrosocarbazole searching for optimal reaction conditions. 9-Nitrosocarbazole is readily nitrated in acetic acid solution at room temperature. Nitration of 9-acetylcarbazole requires prolonged heating; in acetic anhydride solution the reaction occurs at room temperature. 9-Tosylcarbazole is resistant to the action of nitric acid in boiling acetic acid medium. The substrate can be recovered unchanged after heating for 15 h. Nitration can be achieved in boiling acetic anhydride.

3-Nitro-9-nitrosocarbazole is the main product of the reaction and was isolated in a pure state in 65% yield. The crystalline product obtained from 9-acetylcarbazole consists of 3-nitro and 2-nitro-9-acetylcarbazole in an approximate ratio of 2:1. The compounds cannot be separated by repeated crystallisations. Nitration of 9-tosylcarbazole gives mainly the 3-nitro derivative but the crude product cannot be separated from two other isomers.

Isomer distribution was established by preparative layer chromatography. The compounds mentioned above were nitrated with nitric acid, then the acyl groups were removed by alkaline hydrolysis and the isomeric nitrocarbazoles were separated by chromatography (results are given in the Table 1). No trace of 4-nitrocarbazole was detected in any case. 9-Acetyl and 9-tosylcarbazole gave large amounts of 2-nitrocarbazole, but no 9-nitrosocarbazole.

The rate of 9-nitrosocarbazole nitration and the isomer distribution resemble those of carbazole and differs markedly from the behaviour of 9-acetylcarbazole. These differences can be easily explained if we assume that 9-nitrosocarbazole is oxidised with nitric acid to 9-nitrocarbazole which rearranges rapidly yielding the mixture of 1- and 3-nitrocarbazole.

This scheme corresponds with the presence of 1-nitro and 3-nitrocarbazole in the reaction mixture: the first one does not form 9-nitroso derivative and

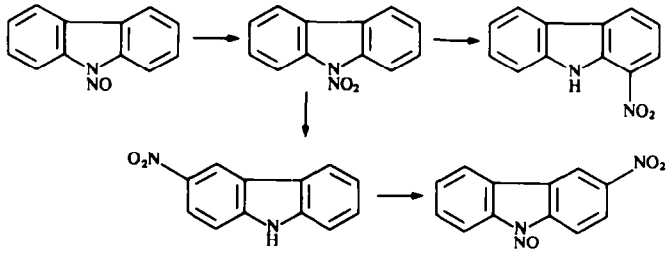
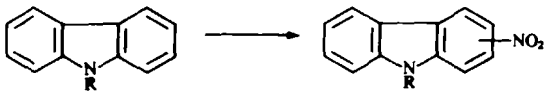


Table 1. Isomer distribution of mononitrocarbazoles



R	Reaction conditions	1-NO_2	2-NO_2	3-NO_2
Alkyl	HNO_3 d 1.52, stoichometric amount, AcOH, 3 h at the temp. of 50°C.	10%	-	90%
Ac	HNO_3, 100% excess, AcOH, 5 h at 95°C.	10%	48%	42%
Ts	HNO_3, 100% excess, Ac_2O, 3.5 h at the boiling point.	28%	19%	53%
H	HNO_3, stoichometric amount, Ac_2O, 3 h at 50°C.	34%	-	66%
H	HNO_3, stoichometric amount, AcOH, 5 h at the room temperature	33%	-	67%
H	$NaNO_2$, 2 moles per mole of the substr., AcOH, 2 h on the boiling water bath.	36%	-	64%
H	AcOOH, 3 moles per mole of the substr., AcOH, 5 h at 25°C	34%	-	66%
H	HNO_3, stoichometric amount, AcOH, 3 h at 50°C	31%	-	69%

the second is not converted quantitatively because of some loss of nitric oxides during the addition of nitric acid. The same process can be carried out using nitric oxide (sodium nitrite in acetic acid solution) as the oxidizing agent. The isomer distribution is very similar to that observed in the nitration of 9-nitrosocarbazole and carbazole although a direct substitution in the aromatic ring is impossible under such conditions.

Similar schemes can be adopted for the explanation of some literature data Drake *et al.* reported that 1-bromocarbazole was resistant to nitrous acid and only under drastic conditions the formation of traces of unidentified C-nitro derivatives was observed. However, one exception was noted: 1-bromo-3-nitrocarbazole was produced almost at once if the cold solution of the substrate in acetic acid was treated with an excess (3 equivalents) of sodium nitrite.[8]

An analogous reaction path (nitrosation, oxidation and nitroamine rearrangement) explains the difference in the product distribution of nitration of 1,3,6,8-tetra-t-butylcarbazole.[9] With nitric acid, only nitrodealkylation occurs; the 1-nitro derivative is the minor product. N-Nitrosation is reversible because of the steric hindrance but oxidation of the unstable intermediate with an excess of nitrous anhydride causes formation of the 9-nitro derivative which rearranges readily.

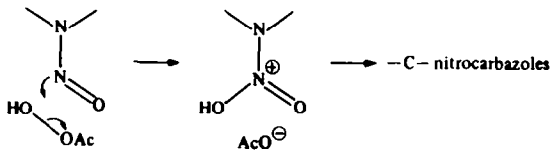
In our opinion nitration of carbazole is also an indirect process. Two alternative pathways should be taken into consideration. The first one involves nitrosation of carbazole with residual nitrous oxide contaminating nitric acid, Fischer–Hepp rearrangement and oxidation of 3-nitrosocarbazole. The second one closely resembles the mechanism of nitration of 9-nitrosocarbazole and involves formation and rearrangement of 9-nitrocarbazole. Fischer–Hepp rearrangement as the key step of the process providing nitrocarbazoles was postulated by Drake *et al.*[8] Their assumption seems to be not valid since it was established that the rearrangement of 9-nitrosocarbazole gives 3-nitrosocarbazole as the only compound and moreover the product is very resistant to oxidation.[10]

In order to support our assumption it should be proved that 9-nitrocarbazole can be formed under the condition used and that its rearrangement gives the mixture of 1-nitro and 3-nitrocarbazole in a ratio of approximately 3:7. In fact nitration of 1,3,6,8-tetrachlorocarbazole gives the product containing the nitro group connected to the pyrrole nitrogen. The reaction was performed in boiling acetic acid or anhydride solution with an excess of nitric acid. On the basis of spectral data to the compound isolated the structure of 1,3,6,8-tetrachlorocarbazole–9-nitro-1,3,6,8-tetrachlorocarbazole 1:1 complex was assigned.

In the mass spectrum two sets of peaks were observed in the regions of *m/e* 348–352 and 303–307. Their relative intensities were consistent with the values calculated for the parent ions $[C_{12}H_4Cl_4N_2O_2]^{+\cdot}$ and $[C_{12}H_5Cl_4N]^{+\cdot}$. Two other significant sets at *m/e* 318–322 and 302–306 could be attributed to fragment ions (M–NO and M–NO_2 respectively) of the nitrated part of the complex molecule. The aromatic protons of 1,3,6,8-tetrachlorocarbazole (TCC) show in the NMR spectrum a simple pattern consisting of two doublets at δ 8.33 and δ7.77 ppm. In the spectrum of the complex these peaks are slightly shifted upfields (7.93 and 7.68 respectively) and an additional pair of signals at δ 8.46 and 7.77 ppm is observed. The sharp singlet of the pyrrole proton is shifted from 12.00 in the TCC spectrum to 8.14 in the case of the complex.

Whatever is responsible for the unusual stability of the complex, the hydrogen bond seems to play an important role. Interaction between the pyrrole proton and the nitramino group gives rise to a splitting of the absorption band in the IR at 3420 cm^{-1} (TCC) into a doublet with maxima at 3370 and 3405 cm^{-1} observed in the spectrum of the complex. The strong bands at 1295 and 1545 cm^{-1} characteristic of the NO_2 stretching vibrations are outside of the region in which absorption of C-nitrocarbazoles is usually observed (1320–1350 and 1490–1510 cm^{-1}). 9-Nitrocarbazole described by Welzel[11] shows the corresponding bands at 1276 and 1540 cm^{-1}.

The synthesis of 9-nitrocarbazole is not an easy task; the Welzel's procedure gave unsatisfactory results. At present we have no effective route to 9-nitrocarbazole but the results of oxidizing 9-nitrosocarbazole (see Table 1) with peracetic acid confirms that rearrangement of 9-nitrocarbazole gives the same 1-nitro to 3-nitrocarbazole ratio as observed in the case of carbazole nitration. It seems possible that acetic acid is not strong enough to cause nitramine rearrangement. Considering the known mechanism of oxidation with peracids it should be expected that 9-nitrosocarbazole is converted into the protonated form of 9-nitrocarbazole which rearranges rapidly. The results should be the same as in the case of the acid catalysed nitramine rearrangement.



EXPERIMENTAL

3-Nitro-9-tosylcarbazole. The mixture of 42.45 g (0.20 mol) of 3-nitrocarbazole, 200 ml of acetone and 11.20 g (0.20 mole) of potassium hydroxide as 33% aqueous solution was treated with 38.00 g (0.20 mole) of tosyl chloride dissolved 150 ml of acetone. It was stirred at the room temp until deep purple colour ceases (about 0.3–0.5 h). The precipitate was collected by filtration, washed with water and acetone, and crystallised from dimethylformamide (500 ml). 3-Nitro-9-tosylcarbazole (53.50 g–73%) was obtained as light yellow needles, m.p. 215–216°. (Found: C, 62.41; H 3.99% Calc. C, 62.28; H 3.86%.) IR(KBr): 710, 740, 766, 770, 820, 890 (out of plane hydrogen wagging conjugated with nonplanar deformation of the nitro group); 1160, 1320, (SO_2 stretch); 1330, 1510 (NO_2 stretching vibrations).

Nitration of 9-tosylcarbazole. The soln of 6.42 g (0.02 mole) of 9-tosylcarbazole and 1.7 ml (100% excess) of nitric acid in 50 ml of acetic anhydride was refluxed for 3.5 h. After cooling to −20° it deposited 4.00 g of the crude product m.p. 195–205°. Crystallisation from acetic anhydride yielded 3.85 g (53%) of 3-nitro-9-tosylcarbazole m.p. 206–213°. (Found: C, 62.42; H 4.07% Calc. C, 62.28; H 3.86%.) Further crystallisation from dimethylformamide or acetic anhydride did not influence on the melting point. Alkaline hydrolysis gave 3-nitrocarbazole contaminated with 1-nitro and 2-nitro isomers.

9-Tosylcarbazole (1.6069 g–5 mmole) was nitrated as above. The reaction mixture was evaporated to dryness, the residue was dissolved in acetone (50 ml), 10% aqueous potassium hydroxide was added and the solution refluxed for 3 h. Diluted (1%) hydrochloric acid was added, acetone was distilled off and the precipitate was collected by filtration, dried and dissolved in 20 ml of tetrahydrofuran. The mixture was chromatographed on 20 plates (20 × 20 cm) covered with 1 mm thick layer of silicagel (Kieselgel G, typ 60, Merck) in benzene-n-heptane 2:1 system (double development). Four zones were collected and extracted with acetone. Evaporation of the solution gave as follows (in the order of decreasing R_f values): carbazole (0.1420 g–0.85 mmole), m.p. and mixed m.p. 242–243° (benzene–iso-ōctane); 1-nitrocarbazole (0.2022 g–0.95 mmole), m.p. and mixed m.p. 189–190° (after sublimation); 2-nitrocarbazole (0.1398 g–0.66 mmole), m.p. and mixed m.p. 174–175° (subl); and 3-nitrocarbazole (0.3790 g–1.79 mmole), m.p. and mixed m.p. 213–215° (AcEt).

3-Nitro-9-acetylcarbazole. To the mixture of 70.0 g (0.33 mole) of 3-nitrocarbazole and 350 ml of acetic anhydride 0.1 ml of boron trifluoride etherate was added. The thick paste was warmed to the b.p. and cooled. The crude product (66.15 g) was collected by filtration and crystallised from dimethylformamide (330 ml) yielding 60.40 g (72%) of 3-nitro-9-acetylcarbazole as the brown plates. m.p. 237–238°. (Found: C, 65.95; H 4.01 Calc. C, 66.13; H 3.94%.) IR(KBr): 725, 760, 780, 785, 840 (nonplanar deformations of aromatic protons and the nitro group); 1310, 1530 (NO_2 stretch); 1705 (carbonyl band). MS, *m/e*: 255(5.8), 254(32.6, M^+), 213(13.5), 212(100.0), 182(24.5), 166(45.2), 165(12.9, 164(18.1), 154(8.4), 149(26.8), 43(48.4).

Nitration of 9-acetylcarbazole. To the soln of 10.46 g (0.05 mole) of 9-acetylcarbazole in 100 ml of acetic anhydride 2.1 ml (0.05 mole) of nitric acid dissolved in 50 ml of anhydride was added. The mixture was heated to the boiling point and cooled. A yellow, crystalline solid (6.65 g), m.p. 189–213° was collected and crystallised from 450 ml of acetic acid. The nitro compound (5.50 g–43%) had m.p. 190–221°. Recrystallisation from xylene gave well shaped crystals m.p. 194–229°. (Found: C, 66.17; H 4.10% Calc. C, 66.13; H 3.94%.) The crude product, m.p. 189–213°, from the reaction described above (0.6346 g, 2.5 mmole) was dissolved in 1% methanolic potassium hydroxide and refluxed for 0.5 h. Bright-red solution was neutralised with 1% hydrochloric acid, and methanol was distilled off. The yellow precipitate was collected by filtration, dried and dissolved in 20 ml of tetrahydrofurane. Preparative thin layer chromatography was performed as before and gave 3-nitrocarbazole (0.3480 g, 1.64 mmole), 2-nitrocarbazole (0.1570 g, 0.74 mmole) and traces of 1-nitrocarbazole (0.0030 g, 0.014 mmole).

To the solution of 9-acetylcarbazole (2.0924 g, 10 mmole) in acetic acid kept on the boiling water bath the solution of nitric acid (7.85 ml, c = 1.40 mole/l^{-1}) was added. The mixture was heated on the boiling water bath (95–96°) for 5 h and evaporated to dryness. The residue was dissolved in alkaline acetone, refluxed and neutralised. Compounds isolated by TLC were as follows: 3-nitrocarbazole (0.6759 g, 3.20 mmole), 2-nitrocarbazole (0.7664 g, 3.60 mmole), 1-nitrocarbazole (0.1580 g, 0.75 mmole). The compound of the highest R_f value (carbazole) was not isolated quantitatively.

3-Nitro-9-nitrosocarbazole. 3-Nitrocarbazole (6.39 g, 30 mmole) was dissolved in 120 ml of boiling acetic acid, the solution was cooled to 30–40° and sodium nitrite (2.76 g, 40 mmole) was added. The mixture was stirred for 1 h at a temperature of 70°; isolation of copious precipitate was observed. It was collected by filtration, washed with methanol and dried. The crude product (6.65 g, m.p. 145–150°) was dissolved in 300 ml of butanone, the solution was filtered and cooled. 3-Nitro-9-nitrosocarbazole (4.75 g, 66%) was obtained as the brown needles m.p. 166–168° with decomposition. (Found: C, 59.91; H 2.99% Calc. C, 59.75; H 2.92%.) IR(KBr): 725, 760, 780, 840 (nonplanar deformations of aromatic protons and the nitro group); 1310, 1530 (NO_2) stretch); 1440 (NO stretching vibration); 3050 (aromatic C–H stretch). MS, *m/e*: 242(3.8), 241(13.5, M^+), 222(11.5), 211(90.4), 210(86.5), 204(9.6), 181(32.7), 167(13.5), 166(52.9), 165(28.8), 153(46.1), 150(13.5), 149(100.0).

Nitration of 9-nitrosocarbazole. To the soln of 9.81 g (0.05 mole) of 9-nitrosocarbazole in 100 ml of acetic acid 0.05 mole of nitric acid (as 1.40 mol per liter solution in acetic acid) was added. The mixture was left for 2 h at the room temperature. The precipitate was collected by filtration, washed with methanol and dried. 3-Nitro-9-nitrosocarbazole (9.35 g–73%) was obtained; m.p. 156–160°. Crystallisation from butanone gave 7.84 g (65%) of brown-yellow needles melting at 165–168° with decomposition. (Found: C, 59.68; H 3.07 Calc. C, 59.75; H 2.92%.) 9-Nitrosocarbazole (1.9620 g–10 mmole) dissolved in 100 ml of acetic acid warmed to 50° was treated with the equimolar amount of nitric acid (7.15 ml of the solution c–1.40 N). The mixture was maintained for 1 h at 50° and evaporated in vacuum. The crude product was hydrolysed and chromatographed as described before. The compounds isolated were as follows: 1-nitrocarbazole (0.3894 g–1.84 mmole), m.p. 189–190° (subl.); 3-nitrocarbazole (0.7834 g–3.70 mmole), m.p. 214–215° (AcEt); dinitrocarbazoles (0.6428 g–2.50 mmole, m.p. > 360° (DMF).

Oxidation of 9-nitrosocarbazole. The soln of peracetic acid (12 ml, c=2.5 N) in acetic acid was added to 9-nitrosocarbazole (1.9620 g–10 mmole) dissolved in 100 ml of acetic acid. The mixture was maintained at the temperature of 25° for 24 h and worked up as before. The compounds isolated were as follows: unreacted 9-nitrosocarbazole (0.4028 g–2.0 mmole), m.p. 80–81° (Et_2O); carbazole (0.2465 g–1.3 mmole), m.p 243—245° (subl.); 1-nitrocarbazole (0.3810 g–1.8 mmole), m.p. 188–189° (subl.); 3-nitrocarbazole (0.7499 g–3.55 mmole, m.p. 214–215° (AcOH).

9-Nitrosocarbazole (1.9620 g–10 mmole) was dissolved in 100 ml of acetic acid and 2.10 g (0.03 M) aq conc sodium nitrite was added. The mixture was warmed for 2 h on the boiling water bath. The solvent was distilled off under reduced pressure and the residue was chromatographed. 9-Nitrosocarbazole (0.0630 g–0.3 mmole), m.p. 78–79° (Et_2O); carbazole (0.1701 g–1.0 mmole), m.p. 242–243° (subl); 1-nitrocarbazole (0.5196 g–2.45 mmole), m.p. 189–190° (subl.), and 3-nitrocarbazole (0.5196 g–4.4 mmole), m.p. 213–215° (AcEt) were isolated.

Nitration of 1,3,6,8-tetrachlorocarbazole. 1,3,6,8-Tetrachlorocarbazole (3.05 g–0.01 M) was dissolved in 120 ml of acetic anhydride and the solution cooled to the room temperature. Nitric acid d 1.52 (1.25 ml–0.03 M) was added and the suspension refluxed. The brown solution deposited yellow needles (m.p. 264–265°) when cooled. They were collected by filtration, washed with methanol and dried. The crude product (2.85 g) was crystallised from 200 ml of toluene yielding 2.55 g (73%) of the 1,3,6,8-tetrachlorocarbazole/1,3,6,8-tetrachloro-9-nitrocarbazole complex. (Found: C, 43.82; H, 1.70% Calc. C, 44.00; 1.41%.) (IR(KBr): 860, 870 (out of plane hydrogen wagging, isolated protons); 1295, 1545 (stretching vibrations of the nitro group); 3370, 3405 (pyrrole proton stretching vibrations). MS, *m/e*: 352(23.6), 251(7.3), 350(49.1), 349(6.2), 348(37.2), 322(3.6), 320(7.3), 318(6.2), 307(47.3), 306(33.4), 305(100.0), 304(51.0), 303(80.0), 302(28.7). NMR(DMSO-d_6): 1.54, d J-2Hz, 2H (4′,5′-protons); 1.86, s, 1H (pyrrole proton); 2.07, d J-2Hz, 2H (4,5-protons)- 2.23; d J-2Hz, 2H (2′,7′-protons); 2.32, d J-2Hz (2,7-protons).

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