

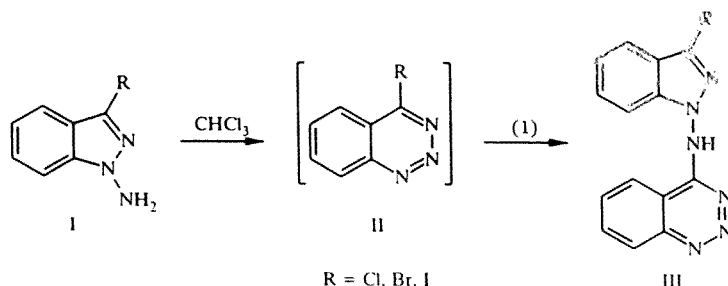
SYNTHESIS AND SOME PROPERTIES OF 1-AMINO-3-NITROINDAZOLE

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By treating 3-nitroindazole with hydroxylamine-O-sulfonic acid in basic medium, we have obtained its 1-amino derivative. We have observed that in chloroform solution in the presence of triethylamine, it is slowly converted to 1-ethylideneamino-3-nitroindazole. We discuss a possible mechanism for this unexpected reaction.

Recently we observed a new oxidative reaction in the 1-aminoindazole series [1]. We found that 1-amino-3-haloindazoles I in chloroform or carbon tetrachloride solution over the course of several days are converted to 4-(3-halo-1-indazolyl)amino-1,2,3-triazines III.

When treated with these solvents, which are soft oxidants [2,3], the amino group in compound I is preferentially oxidized to N-nitrene, which undergoes recyclization to the corresponding 4-halo-1,2,3-benzotriazine II (compare with [4,5]). The latter, due to the high mobility of its halogen, then reacts with the starting amine to form compounds III. In this connection, the question arises of which of the two main steps of this reaction is rate-determining. If the first oxidative step is rate-determining, then introduction of acceptor groups into position 3 of the 1-aminoindazole molecule should hinder or even completely inhibit it. If the step of hetarylation of the amino group in compound I is the slower step, then conversely an increase in mobility of the substituent R in the intermediate triazine II will promote more facile occurrence of the reaction. A very convenient compound for testing this hypothesis might be the previously unknown 1-amino-3-nitroindazole (V). On the one hand, as a strong electron acceptor, the NO₂ group should hinder the first step. On the other hand, as a good leaving group in S_N2Ar reactions, it will be substituted in the second step of the reaction significantly more easily than the halogen [6].



1-Amino-3-nitroindazole was obtained by amination of 3-nitroindazole (IV) by hydroxylamine-O-sulfonic acid in basic borate buffer (these amination conditions are suggested in [7] for poorly nucleophilic N-anions). The yield of amine V was 78%. Like other 1-aminoindazoles, it easily forms azomethines such as VIa,b on heating with aromatic aldehydes. In contrast to 1-amino-3-haloindazoles I, the amine V was stable in storage. Its chloroform solution also does not change over the course of 2-3 weeks, although after that decomposition products gradually appear. But if we add triethylamine to the solution of the amine in chloroform, a yellow compound begins to slowly accumulate in the mixture which has proven to be 1-ethylideneamino-3-nitroindazole (VII). Its yield after 40 days reached 63%. The structure of compound VII was confirmed by spectral data, including the mass spectrum, and also by its reduction by sodium borohydride to 1-ethylamino-3-nitroindazole (VIII).

10 ml acetic anhydride were added all at once and the temperature was raised to 45–50°C. The precipitate first dissolved, but after ~ 10 min yellow crystals fell out of solution. The mixture was stirred for 30 min, on cooling 200 ml of water were added, and then the precipitate was filtered off, washed with water, and dried in air. Yield, 9.2 g. The crude material was ground with 100 ml ether, the insoluble part (5.2 g) was practically pure 3-nitroindazole. The brownish-red oily residue obtained after evaporation of the ether was chromatographed on a column with silica gel ($h = 30$ cm, $d = 3$ cm), eluent chloroform—ethylacetate, 3:1. The fraction with R_f 0.6 was collected. Yield, 0.8 g. The total yield of 3-nitroindazole was 6.0 g (50%). Greenish-yellow crystals with mp 210–211°C (from aqueous ethanol); according to the data in [7] mp 205°C. IR spectrum (Vaseline oil): 3228 (NH), 1531, 1374 cm^{-1} (NO_2). PMR spectrum ($\text{DMSO}-D_6$): 7.53 (1H, td, 5-H); 7.62 (1H, td, 6-H); 7.80 (1H, d, 7-H); 8.17 (1H, d, 4-H); 14.50 ppm (1H, broad s, NH).

1-Amino-3-nitroindazole (V). 1.7 g (15 mmoles) hydroxylamine-O-sulfonic acid was added to a solution of 0.82 g (5 mmoles) 3-nitroindazole and 1.2 g (30 mmoles) sodium hydroxide in 25 ml borate buffer (pH 10). The mixture was stirred for 4 h at 60°C. A brown precipitate gradually fell out, the pH of the solution decreased down to 9. On cooling, the crystals were filtered off, washed with water, and dried in air. Yield, 0.75 g. The crude material was dissolved in 30 ml ethylacetate and passed through a column with silica gel ($h = 25$ cm, $d = 2.5$ cm), eluent chloroform—ethylacetate, 3:1. The first fraction with R_f 0.7 was collected. Yield, 0.7 g (78%). Brownish-red crystals with mp 190–192°C (from ethanol). IR spectrum (Vaseline oil): 3336, 3214 (NH_2), 1642 (ring), 1527, 1387 cm^{-1} (NO_2). PMR spectrum (CDCl_3): 5.52 (2H, broad s, NH_2); 7.48 (1H, td, 5-H); 7.58 (1H, td, 6-H); 7.74 (1H, dd, $J_6 = 8.50$ Hz, $J_7 = 0.88$ Hz, 7-H); 8.24 ppm (1H, dd, $J_4 = 8.20$ Hz, $J_5 = 0.88$ Hz, 4-H). Found, %: C 47.30; H 3.50; N 31.61. $\text{C}_7\text{H}_6\text{N}_4\text{O}_2$. Calculated, %: C 47.19; H 3.37; N 31.46.

1-Benzylideneamino-3-nitroindazole (VIa). A solution of 0.18 g (1 mmoles) amine V and 0.1 ml (1 mmoles) benzaldehyde in 5 ml ethanol was boiled for 2 h. On cooling, the brown residue was filtered off, washed with cold ethanol and ether. Yield, 0.2 g (75%). Orange needles with mp 180–182°C (from butanol). IR spectrum (Vaseline oil): 1605 (ring), 1534, 1387 cm^{-1} (NO_2). PMR spectrum (CDCl_3): 7.54 (4H, m, 5-H, 3', 4', 5'-H); 7.64 (1H, td, 6-H); 8.00 (3H, m, 7-H, 2', 6'-H); 8.31 ppm (1H, dd, $J_5 = 8.20$ Hz, $J_6 = 1.17$ Hz, 4-H). Found, %: C 63.30; H 3.82; N 20.96. $\text{C}_{14}\text{H}_{10}\text{N}_4\text{O}_2$. Calculated, %: C 63.16; H 3.76; N 21.05.

1-(4-Nitrobenzylidene)amino-3-nitroindazole (VIb). A solution of 0.25 g (1.4 mmoles) amine V and 0.21 g (1.4 mmoles) *p*-nitrobenzaldehyde in 5 ml glacial acetic acid was boiled for 30 min. On cooling, the precipitate was filtered off, washed with ethanol and ether. Yield 0.35 g (80%). Yellow crystals with mp 287–289°C (from DMF). IR spectrum (Vaseline oil): 1600 (ring), 1520, 1493, 1373, 1344 cm^{-1} (NO_2). Found, %: C 53.89; H 3.06; N 22.46. $\text{C}_{14}\text{H}_9\text{N}_5\text{O}_4$. Calculated, %: C 54.02; H 2.90; N 22.51.

1-Ethylideneamino-3-nitroindazole (VII). A solution of 0.1 g (0.56 mmoles) amine V in 10–15 ml chloroform containing five drops of triethylamine was allowed to stand at room temperature for 30 days. Then the solution was evaporated down to a small volume and passed through a column with silica gel ($h = 15$ cm, $d = 2.0$ cm), eluent chloroform. The first yellow fraction with R_f 0.45 was collected: 1-ethylideneamino-3-nitroindazole (VII). Yield, 0.07 g (63%). Dark yellow prisms with mp 136–138°C (from ethanol). UV spectrum (methanol), λ_{max} , nm (lge): 231 (4.38), 349 (4.13). IR spectrum, (Vaseline oil): 1518, 1373 cm^{-1} (NO_2). PMR spectrum (CDCl_3): 2.29 (3H, d, $J = 5.57$ Hz, CHCH_3); 7.50 (1H, td, 5-H); 7.59 (1H, td, 6-H); 7.87 (1H, d, $J_6 = 8.50$ Hz, 7-H); 8.26 (1H, d, $J_4 = 8.20$ Hz, 4-H); 8.80 ppm (1H, q, $J = 5.57$ Hz, CHCH_3). Mass spectrum, m/z (I_{rel} , %): 204 (100), M^+ , 158 (20) [$\text{M}-\text{NO}_2$] $^+$, 131 (19), 117 (27), 102 (17), 90 (27), 77 (15), 62 (6), 51 (10), 44 (15). Found, %: C 53.65; H 4.49; N 28.63. $\text{C}_9\text{H}_8\text{N}_4\text{O}_2$. Calculated, %: C 52.94; H 3.92; N 27.45.

When chloroform is replaced with carbon tetrachloride, the reaction does not occur to an appreciable degree. This is probably explained by the very low solubility of amine V in carbon tetrachloride.

1-Ethylamino-3-nitroindazole (VIII). 0.038 g (1 mmole) NaBH_4 was added in portions to a suspension of 0.2 g (1 mmole) compound VII in 10 ml isopropanol. The mixture was allowed to stand at room temperature for 24 h, after which it was evaporated to dryness. The residue was dissolved in 10 ml chloroform and passed through a column with silica gel ($h = 15$ cm, $d = 2.0$ cm), eluent chloroform. The fraction with R_f 0.33 was collected. Yield, 0.15 g (73%). Pale yellow needles with mp 100–102°C (from octane). IR spectrum (Vaseline oil): 3287 (NH), 1618, 1584 (ring), 1515, 1376 cm^{-1} (NO_2). PMR spectrum (CDCl_3): 1.13 (3H, t, $^3J = 7.32$ Hz, CH_2CH_3); 3.42 (2H, m, CH_2CH_3); 5.32 (1H, m, NH); 7.46 (1H, td, 6-H); 7.55 (1H, td, 5-H); 7.70 (1H, d, $J_6 = 8.50$ Hz, 7-H); 8.24 ppm (1H, d, $J_4 = 8.20$ Hz, 4-H). Found, %: C 52.52; H 4.91; N 27.31. $\text{C}_9\text{H}_{10}\text{N}_4\text{O}_2$. Calculated, %: C 52.43; H 4.85; N 27.18.

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