SUBSTITUTION IN THE INDOLE BENZENE RING

XI. Synthesis of Substituted 5-Nitro-6-aminoindoles*

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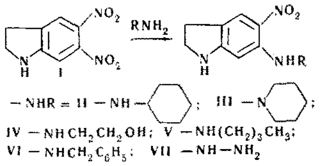
It has been shown that 5, 6-dinitroindoline and its N-acetyl derivative undergo nucleophilic substitution when reacting with primary and secondary amines, thereby substituting a nitro group in position 6 by an amine residue.

5, 6-Dinitroindoline and its acetyl derivative, previously synthesized by us [2], as well as other o-dinitro compounds react with primary and secondary amines, thus substituting a nitro group by an amine residue. Among the amine components employed were n-butylamine, cyclohexylamine, ethanolamine, benzylamine, hydrazine hydrate, and piperidine.



The yields of compounds II–VII attained 70–90%. The reactions of N-acetyl-5, 6-dinitroindoline (VIII) with amines led to lower yields, since prolonged heating (4–6 hr), besides the substitution of a nitro group by an amine residue, also brought about the separation of the acetyl group. Thus, for instance, after a 2-hr heating with n-butylamine, the yields of 5-nitro-6-butylamino-1-acetylindoline amounted to only 30%, while a 6-hr heating produced an 82% yield of a compound without the acetyl group. The same may be said of hydrazine hydrate. A 30-min heating with this compound led to a 48% yield of the acetyl-free product, while a 4-hr boiling produced free 5-nitro-6-hydrazinoindoline only.

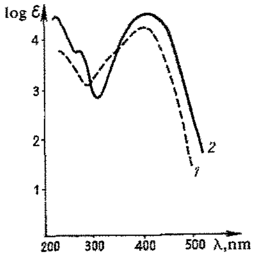


Fig. 1. UV Spectra: 1)-5-nitroindoline; 2)-6-nitroindoline.

The substitution reaction of free 5, 6-dinitroindoline and its N-acetyl derivative proceeded at one and the same positions, as indicated by the following transformations.

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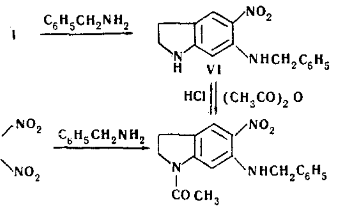
*For part X, see [1].



As in the aromatic amines series [3–5], in 5, 6-dinitroindoline the more mobile nitro group is in meta position with respect to the amino group. This led in our case to the formation of 5-nitro-6-aminoindolines. The UV spectra of several indoline derivatives confirmed this statement. In the spectrum of 5-introindoline, the nitro group in the p-position with respect to the ring nitrogen determined the high intensity of the long—wave absorption band. The nitro group in 6-nitroindoline is in the m-position and the shortwave band became the more intense (Fig. 1).

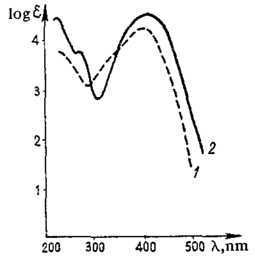


Fig. 2. UV Spectra: 1)-5-nitroindoline; 2)-5-nitro-6-cyclohexylaminoindoline.

In the UV spectra of the nitroaminoindolines obtained, we observed, in all cases, the presence of a clearly pronounced long-wave band of high intensity and a low-intensity, shortwave band. This testified to the presence of a nitro group in the p-position with respect to the indoline ring nitrogen, and thus confirmed the substitution of a nitro group in position 6 (Fig. 2).

EXPERIMENTAL

5-Nitro-6-cyclohexylaminoindoline (II). A mixture of 10 g (40.5 mM) of 5, 6-dinitroindoline and 15 ml (123.5 mM) of cyclohexylamine was slowly heated to the boiling point of cyclohexylamine. The heating was continued at this temperature for 1.5–2 hr. The mixture was then cooled, and the product was precipitated with ether (350–400 ml). Yield 14.4 g (91%). Dark-colored crystals with a violet lustre, forming a yellow powder when ground, mp. 184.5–185.5° C (ex ethanol). UV spectrum (in methanol), λ_{max}, nm (log ε): 225 (4.41); 275 (3.69); 415 (4.38). Found, %: C 64.05; H 7.24. Calculated for $C_{14}H_{19}N_3O_2$, %: C 64.34; H 7.33.

5-Nitro-6-piperidylaminoindoline (III). A mixture of 0.5 g (2 mM) of 5, 6-dinitroindoline and 2 ml (20 mM) of piperidine was heated at the boiling point of piperidine for about 1.5 hr. The reaction mass was cooled by dilution with a large quantity of water. When the separated oil was stirred with water, cinnamon-colored crystals were obtained. Yield 0.6 g (80%), mp 103–104° C (ex heptane). UV spectrum (in methanol), λ_{max}, nm (log ε); 236 (4.07); 296 (3.80); 400–430 (4.06). Found, %: C 63.44; H 6.92; N 16.96. Calculated for $C_{13}H_{17}N_3O_2$, %: C 63.14; H 6.93; N 16.99.

5-Nitro-6-hydroxyethylaminoindoline (IV). A mixture of 1 g (4 mM) of 5, 6-dinitroindoline and 10 ml (164 mM) of monoethanolamine was heated for 1 hr on a boiling water-bath. Upon cooling, the precipitate formed was filtered-off and recrystallized ex methanol with the addition of activated charcoal. Yield 0.82 g (76.5%). The product crystallized in lustrous, orange-colored needles, mp 193–194° C (ex methanol or nitromethane), readily soluble in dimethylformamide. UV spectrum (in methanol), λ_{max}, nm (log ε): 225 (4.35); 275 (3.68); 415 (4.30). Found, %: C 53.78; H 6.06. Calculated for $C_{10}H_{13}N_3O_3$, %: C 53.80; H 5.87.

5-Nitro-6-butylaminoindoline (V). A) A mixture of 3 g (11.9 mM) of 5, 6-dinitro-N-acetylindoline and 10 ml (101 mM) of n-butylamine was heated at 78° C for 6 hr. When the reaction mass cooled down, the precipitate formed was filtered-off. The yield of V was 2 g (82%). Orange-yellow crystals melting at 143.5–145.0° C (ex aqueous methanol with the addition of activated charcoal). UV spectrum (in methanol), λ_{max}, nm (log ε): 229 (4.25); 282 (3.74). Found, %:

C 61.36; H 7.50. Calculated for $C_{12}H_{17}N_3O_2$, %: C 61.25; H 7.28.

B) A mixture of 5 g (20.1 mM) of 5, 6-dinitroindoline and 10 ml (101 mM) of butylamine was heated to the boiling point of butylamine (77° C) in the course of 4 hr. The precipitate formed on cooling was filteredoff, yielding 3.8 g (69%) of V, melting at 144–145° C (ex aqueous methanol). This product was identical chromatographically to that obtained under (A), and a mixed sample exhibited no melting point depression.

5-Nitro-6-butylamino-1-acetylindoline. A mixture of 3.1 g (12.3 mM) of 5, 6-dinitro-1-acetylindoline and 15 ml (150 mM) of butylamine was boiled for 2 hr on a water-bath and then evaporated to dryness. The residue was treated with 15 ml methanol and the insoluble crystals were filtered-off. Yield 1g (30%), mp 142–143° C (ex methanol with the addition of activated charcoal). Brick-red crystals, insoluble in ether, difficultly soluble in methanol, soluble in acetone and dimethylformamide. UV spectrum (in dimethylformamide), λ_{max}, nm (log ε): 335 (4.39); 440 (4.10); 445–450 (4.07). Found, %: C 60.39; H 7.04. Calculated for $C_{14}H_{19}N_3O_3$, %: C 60.63; H 6.90.

5-Nitro-6-benzylaminoindoline (VI). A mixture of 1.5 g (5.95 mM) of 5, 6-dinitroindoline and 6 ml (56 mM) of benzylamine was heated on a boiling water-bath for 7 hr. When cooled down, the reaction mass was treated with 200 ml ether. The precipitate formed was filtered-off and washed with 200 ml ether. Yield 8.2 g (90%), mp 172.5–173.5° C (ex ethanol with the addition of activated charcoal).

Cinnamon-color needles, becoming a yellow powder when ground, insoluble in ether, difficulty soluble in methanol, soluble in acetone and dimethylformamide. UV spectrum (in dimethylformamide), λ_{max}, nm (log ε): 282 (3.63); 415 (4.28). Found, %: C 66.67; H 5.59. Calculated for $C_{15}H_{15}N_3O_2$, %: C 66.90; H 5.61.

5-Nitro-6-benzylamino-1-acetylindoline. A) A mixture of 8.5 g (0.034 mole) of 5, 6-dinitro-1-acetylindoline and 13 ml (0.122 mole) of benzylamine was heated on a boiling water-bath for 2 hr. Upon cooling, the reaction mass was treated with 200 ml methanol, the precipitate filtered-off and washed with 35 ml ether. Yield 5.6 g (47.8%), mp 221.5–222° C (ex dimethylformamide with the addition of activated charcoal). Orange-color crystals, insoluble in ether, difficultly soluble in methanol, better in acetone and dimethylformamide. UV spectrum (in dimethylformamide), λ_{max}, nm (log ε): 275 (3.72); 340 (4.00); 435 (4.01). Found, %: C 65.52; H 5.60; N 13.39. Calculated for $C_{17}H_{17}N_3O_3$, %: C 65.58; H 5.50; N 13.50.

B) A solution of 0.1 g (0.371 mM) of 5-nitro-6-benzylaminoindoline in 5 ml acetic anhydride was heated on a boiling water-bath for 2.5 hr. Upon cooling, 50 ml water was added to the reaction mixture, and after 2 hr neutralized with an aqueous sodium bicarbonate solution.

The orange-color precipitate formed was filtered-off and washed with 10 ml water. Yield 0.09 g (86.5%), mp 221.5–222° C (ex dimethylformamide). A mixture of this oompound with that obtained by procedure (A) exhibited no melting point depression.

5-Nitro-6-hydrazino-1-acetylindoline. A suspension of 3 g (12 mM) of 5, 6-dinitro-1-acetylindoline in 25 ml ethanol was heated on a water-bath and 3 ml of hydrazine hydrate was added drop by drop. A red precipitate was formed within 10–15 min, and the heating was continued for still 15 min. Upon cooling, the precipitate was filtered off. Yield 1.35 g (48%). Orange-color needles melting at 208–209° C (after double recrystallization ex isopropyl alcohol). UV spectrum (in dimethylformamide), λ_{max}, nm (log ε): 340 (4.04); 440 (3.92). Found, %: C 51.16; H 5.42. Calculated for $C_{10}H_{12}N_4O_3$, %: C 50.84; H 5.12.

5-Nitro-6-hydrazinoindoline (VII). To a mixture of 3 g (12 mM) of 5, 6-dinitro-1-acetylindoline and 0.40 g potash in 20 ml ethanol, 10 ml of hydrazine hydrate was added and the mixture heated for 4 hr on a water-bath. Upon cooling, the precipitate formed was filtered-off. Yield 0.18 g (77%), mp 179–180° C (ex ethanol with the addition of activated charcoal). Yellowish-orange crystals, very soluble in dimethylformamide, more difficultly in water and alcohols. UV spectrum (in dimethylformamide), λ_{max}, nm (log ε): 420 (4.40); Found, %: C 45.59; H 5.18. Calculated for $C_8H_{10}N_4O_2$, % C 49.84; H 5.19.

The chromatographic control of the course of the reaction and of the purity of the compounds obtained was achieved by ascending thin-layer chromatography on a loose aluminum oxide layer of activity II according to Brockmann. The UV spectra were recorded on an SF-4a apparatus.

REFERENCES

1. A. P. Terent'ev, E. V. Vinogradova, V. P. Chetverikov, and V. S. Lenenko, KhGS [Chemistry of Heterocyclic Compounds], 262, 1969.
2. A. P. Terent'ev, E. V. Vinogradova, V. P. Chetverikov, and V. S. Lenenko, KhGS [Chemistry of Heterocyclic Compounds], 258, 1969.
3. P. van Romburgh and C. W. Zahn, Rec. trav. chim., **57**, 437, 1938; C., **11**, 1937, 1938.
4. P. van Romburgh, Rec. trav. chim., **42**, 804, 1923.
5. I. Arcos and I. Miller, J. Am. Chem. Soc., **77**, 3128, 1955.

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