INTRODUCTION OF SUBSTITUENTS INTO THE BENZENE NUCLEUS OF INDOLE

IX. 5,6-Dinitro- and 5,6-Diaminoindolines*

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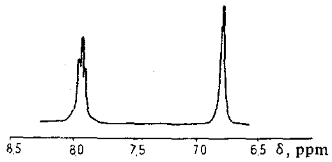
It has been shown that in the nitration of 1-acetyl-6-nitroindoline with nitric acid (d 1.52) in acetic anhydride, the second nitro group enters position 5 of the indoline ring. In the nitration of 5- and 6-acetylaminoindolines, the nitro group enters positions 6 and 5 of the indoline ring, respectively.

In preceding papers [1, 2] it was shown that the introduction of substituents into the benzene ring of indole can be carried out successfully via the stage of indoline with its subsequent dehydrogenation. Nitro derivatives of indoline are of great interest, since by their reduction to the corresponding amines it is possible to pass to various substituted indolines comparatively readily. Only 5- and 6-nitroindolines have been obtained by the nitration of indoline [2]. The nitration of 1-acetyl-5-nitroindoline has given 1-acetyl-5, 7-dinitroindoline [3]. Previously, Japanese scientists [4], having obtained a nitro derivative by the nitration of 1-acetyl-6-diacetylaminoindoline, put forward the hypothesis that the nitro group had entered position 4 of the indoline ring; no proofs of this were given in their paper. Basically, this exhausts the work on the nitration of indoline.



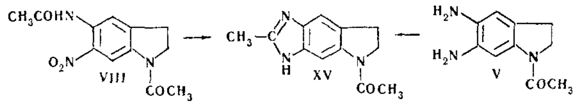
PMR spectrum of the dinitroindoline.

Making use of the analogy with o-toluidine [5], we have carried out the nitration of 1-acetyl-6-nitroindoline (II) in acetic anhydride, obtaining a dinitroindoline (III) with a yield of about 95%. The 1-acetyldinitroindoline obtained was reduced with hydrazine hydrate in the presence of Raney nickel [6] to a 1-acetyldiaminoindoline (V). The yield varied considerably according to the reaction conditions because of the rapid oxidation of the diamine V. However, the performance of the reaction in a current of inert gas enabled the yield of diamine to be raised to 84%. The 1-acetyldiaminoindoline V crystallizes with two molecules of water, losing the water on being heated above 120° C. The dry diamine is completely stable. It can also be characterized in the form of the very stable triacetyl derivative.

The structure of the dinitroindole III was established in accordance with the following scheme on page 197.

1-Acetyl-5- and -6-acetylaminoindolines (VIII, XI) were subjected to nitration, the nitro group entering the o-position with respect to the acetylamino group in both cases. After the reduction of the nitro group to an amino group and acetylation, 1-acetyl-5, 6-diacetylaminoindoline (XIV) was obtained. The XIV obtained in the three ways proved to be identical in chromatographic behavior, melting point (mixtures giving no depression), and UV and IR spectra.

In addition, by the reduction of 1-acetyl-5-acetylamino-6-nitroindoline (VIII) with stannous chloride in hydrochloric acid, we obtained a 55% yield of 1-acetyl-6-methylindolino[5, 6-d]imidazole (XV), which can also be obtained by the reaction of 1-acetyl-5, 6-diamino-indoline (V) with acetic acid.



The structure of the dinitroindoline III was also confirmed by its PMR spectrum. Only the part of the spectrum corresponding to the resonance absorption of the protons of the benzene ring of the dinitroindoline was recorded.

The spectrum clearly shows two singlet peaks indicating that the protons are present in the para position to one another. The signal with a chemical shift of 7.9 ppm belongs to the proton present in position 4 and has a fine triplet structure, the spin-spin coupling constant of 1.2 ± 0.1 Hz showing the interaction of the allyl protons of the —HC=HC—CH group (1.2 Hz) which, in our case, corresponds to interaction with the protons in the β-position. The signal of the proton in position 7 is displaced into the region of stronger fields (δ 6.78 ppm) because of the influence of the neighboring amino group.

Thus, it may be considered as completely proved that the nitro group enters positions 5 and 6 of the indoline ring.

EXPERIMENTAL

6-Nitroindoline (I). With stirring and ice-cooling, 59.5 g (0.5 mole) of freshly distilled indoline was added to 200 ml of concentrated sulfuric acid. To the resulting suspension, a mixture of 22 ml (0.5 mole) of HNO_3 (d 1.52) and concentrated H_2SO_4 was added dropwise at a temperature below 5° C. After the end of the addition, the reaction mixture was stirred for another hour and was then poured into water containing ice. The resinuous precipitate that deposited was filtered off and the filtrate was neutralized with 1 *l* of concentrated ammonia

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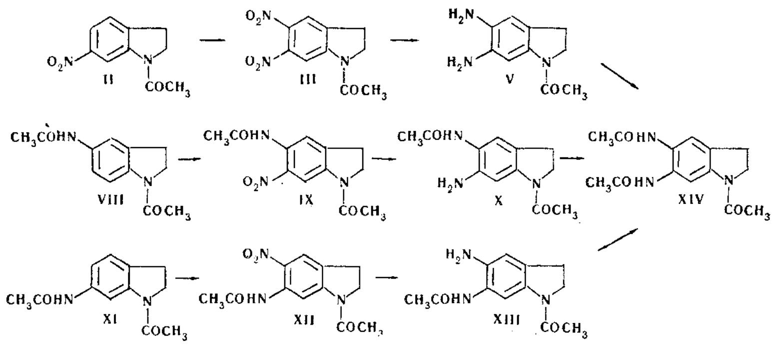
*For part VIII, see [1].



(with ice-cooling). This gave 65.4 g (80%) of bright red crystals; UV spectrum: λ_{max} (log ε) 255 (4.12), 390 nm (3.27) (in methanol). Mp 68–68.5° C (from heptane [2]).

1-Acetyl-6-nitroindoline (II). A mixture of 49 g (0.3 mole) of I and 60 ml (0.6 mole) of acetic anhydride was boiled for 30 min. The reaction mixture was poured into water containing ice, and 60 g (quantitative) of light yellow crystals with mp 153–154° C (from ethanol) [2] was obtained.

1-Acetyl-5, 6-dinitroindoline (III). A suspension of 20.6 g (0.1 mole) of II in 40 ml of acetic anhydride was treated dropwise at 15–20° C with 5 ml of HNO_3 (d 1.52). At the end of the addition, the temperature had risen to 40–50° C and the precipitate then dissolved; on cooling it separated out again. The reaction mixture was poured into water containing ice. The lemon-yellow precipitate that deposited was filtered off and was washed with cold water and then with ether. The crystals were soluble in hot acetic acid and nitromethane, insoluble in ether, carbon tetrachloride, and carbon disulfide, and sparingly soluble in ethanol. Yield 24.0 g (95%), mp 192–192.5° C (after two recrystallizations from toluene). IR spectrum (paraffin oil), cm^{-1}: 1666 (amide carbonyl), 1534, 1348 (nitro group), and 898, 866 (C—H deformation vibrations in a 1, 2, 4, 5-tetrasubstituted benzene). UV spectrum, λ_{max}, nm (log ε): 253 (4.25) and 335 (4.04) (in methanol). Found, %: C 47.86, 47.84; H 3.71, 3.90. Calculated for ($C_{10}H_9N_3O_5$), %: C 47.81; H 3.61.

5, 6-Dinitroindoline (IV). A mixture of 12.6 g of III and 100 ml of concentrated hydrochloric acid was boiled for 1 hr and then the resinuous precipitate was filtered off and the filtrate was neutralized with ammonia. The orange precipitate that deposited was filtered off and washed with water. Yield 8.5 g (78%), mp 208° C (from ethanol). IR spectrum (paraffin oil), cm^{-1}: 1547, 1310 (nitro group), 3398 (secondary amine). UV spectrum, λ_{max}, nm (log ε): 235 (4.42), 262 (4.98), and 390 (4.18) (in methanol). Found, %: C 45.85, 45.65; H 3.62, 3.30. Calculated for ($C_8H_7N_3O_4$), %: C 45.94; H 3.37.

1-Acetyl-5, 6-diaminoindoline (V). To 12.6 g of III was added 300 ml of methanol followed by 25 ml of hydrazine hydrate and then 0.5 g of Raney nickel. Pronounced heating took place. After decoloration the hot solution was filtered rapidly in a current of illuminating gas, cooled, and evaporated in vacuum. A lustrous colorless residue was obtained. Yield 8 g (84%), mp 212–213° C (from methanol); in a sealed capillary. UV spectrum, λ_{max}, nm (log ε): 270–273 (4.11), 318–324 (4.04) (in methanol). Found, %: C 62.73, 62.91; H 6.97, 6.96; N 21.93, 22.16. Calculated for ($C_{10}H_{10}N_3O$), %: C 62.80; H 6.85; N 21.98.

1-Acetyl-5-aminoindoline (VII). To 15 g of 1-acetyl-5-nitroindoline (VI) [7] was added 150 ml of methanol, followed by 25 ml of hydrazine hydrate and 1 g of Raney nickel. After filtration, the filtrate was evaporated in vacuum. This gave colorless crystals, mp 182–184° C (from ethanol), yield 11.8 g (92%).

1-Acetyl-5-acetylaminoindoline (VIII). Heating 9 g of VII in 30 ml of acetic anhydride yielded 11 g (quantitative) of VIII; mp 211–212° C (from ethanol) [2].

1-Acetyl-5-acetylamino-6-nitroindoline (IX). With cooling to 0° C, 3 ml of HNO_3 (d 1.52) was added to a suspension of 2.2 g of substance VIII in 20 ml of acetic anhydride, and then the mixture was stirred for another hour and poured into water containing ice. This gave 2.4 g (91%) of bright orange needles, mp 206–207° C (from ethanol). UV spectrum, λ_{max}, nm (log ε): 262 (4.36) 370–380 (3.35) (in methanol). Found, %: C 55.16, 55.13; H 5.04, 5.02. Calculated for ($C_{12}H_{13}N_3O_4$), %: C 54.75; H 4.98.

1-Acetyl-5-acetylamino-6-aminoindoline (X). With heating, 1 g of compound IX was dissolved in 60 ml of methanol, and 3 ml of hydrazine hydrate and Raney nickel were added. After the end of the reaction, the whole solution was filtered, and the filtrate was evaporated in vacuum to give 0.8 g (90%) of a colorless residue, mp 267–268° C (from ethanol). UV spectrum, λ_{max} nm (log ε): 262 (4.15), 315 (3.91) (in methanol). Found, %: C 61.44, 61.33; H 6.22, 6.29; N 17.54, 17.51. Calculated for ($C_{12}H_{15}N_3O_2$), %: C 61.78; H 6.48; N 18.02.

1-Acetyl-6-acetylaminoindoline (XI). Obtained by the method described previously, mp 271–272° C (from 20% acetic acid) [2].

1-Acetyl-6-acetylamino-5-nitroindoline (XII). With cooling to 0° C, 4 ml of HNO_3 (d 1.52) was added to a suspension of 3 g of compound XI in 30 ml of acetic anhydride. After being stirred for another hour, the mixture was poured onto ice. The precipitate that deposited was filtered off and washed with water. Yield 2.0 g (55%), bright yellow needles, mp 181–181.5° C (from ethanol). UV spectrum, λ_{max}, nm (log ε): 235–237 (4.63), 267 (4.52), 332 (3.97), 348 (3.99) (in methanol). Found, %: C 54.98, 54.91; H 4.98, 4.94. Calculated for ($C_{12}H_{13}N_3O_4$), %: C 54.75; H 4.98.

1-Acetyl-6-acetylamino-5-aminoindoline (XIII). By the usual method, 1 g of XII in 60 ml of methanol with 3 ml of hydrazine hydrate and Raney nickel yielded 0.7 g (79%) of a colorless substance with mp 213° C (from ethanol). UV spectrum: λ_{max}, nm (log ε): 270 (4.26), 312 (3.79) (in methanol). Found, %: C 57.06, 56.90; H 6.82, 6.86. Calculated for ($C_{12}H_{15}N_3O_2 \cdot H_2O$), %: C 57.35; H 6.82.

1-Acetyl-5, 6-diacetylaminoindoline (XIV). a) With heating, 0.5 g of V was dissolved in 0.5 ml of acetic anhydride, and water was added. The precipitate that deposited was filtered off and washed with water to give 0.7 g (quantitative) of a colorless substance with mp 218–219° C (from ethanol). IR spectrum (paraffin oil), cm^{-1}: 1678, 1662, 1630 (amide carbonyls). UV spectrum, λ_{max}, nm (log ε): 268 (4.39) (in methanol). Found, %: C 60.91, 60.73; H 6.19, 6.36. Calculated for ($C_{14}H_{17}N_3O_3$), %: C 61.08; H 6.22.

b) Similarly, from compound X colorless needles with mp 220° C (from ethanol) were obtained in quantitative yield. UV spectrum (λ_{max}, nm) (log ε): 268 (4.30) (in methanol). Found, %: C 61.10, 60.98; H 6.46, 6.51. Calculated for ($C_{14}H_{17}N_3O_3$), %: C 61.08; H 6.22.

c) By the same method, from XIII colorless crystals with mp 218–218.5° C were obtained with a yield of 94%. IR spectrum (paraffin oil), cm^{-1}: 1675, 1660, 1625 (amide carbonyls). Found, %: C 61.27, 61.11; H 6.10, 6.25. Calculated for ($C_{14}H_{17}N_3O_3$), %: C 61.08; H 6.22.

1-Acetyl-6-methylindolino[5, 6-d]imidazole (XV). a) In drops, 9 ml of hydrochloric acid (1 : 1) was added to a mixture of 1.9 g of IX and 6.5 g of stannous chloride in 50 ml of methanol that had been brought to the boil in the water bath. After the end of the reaction, the methanol was distilled off in vacuum, and the residue was treated with 100 ml of water and hydrogen sulfide passed into the solution. After filtration, the filtrate was neutralized with 2 N caustic soda. This gave 0.85 g (55%) of a colorless precipitate with mp 329–331° C (from ethanol). UV spectrum, λ_{max}, nm (log ε): 232 (4.42), 260 (3.90), 270 (3.87), 302 (4.12), 312 (4.14). (In methanol). Found, %: C 67.26, 67.23; H 5.98, 6.18. Calculated for ($C_{12}H_{13}N_3O$), %: C 67.95; H 6.09.

b) A mixture of 1 g of **V** and 20 ml of glacial acetic acid was boiled under reflux for 3 hr. Then the solution was neutralized with caustic soda and the precipitate that had deposited was filtered off. Yield 0.4 g (45%), mp 329–330° C (from ethanol).

The chromatographic monitoring of the course of the reactions and of the purity of the compounds obtained was carried out by thin-layer ascending chromatography in an unfixed layer of alumina of Brockmann activity II. The UV spectra were recorded on an SF-4A instrument, the IR spectra on an IKS-14 instrument, and the NMR spectra on an JNM-4H-100 instrument.

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