

INTRODUCTION OF SUBSTITUENTS INTO THE
BENZENE RING OF INDOLE

XIII.* DINITRO DERIVATIVES OF 2-METHYLINDOLINE

A. P. Terent'ev, † I. G. Il'ina,
and V. G. Bakmutskaya

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A number of dinitro-2-methylindolines (5,6-, 6,7-, and 5,7-) were synthesized by the nitration of nitro-2-methylindoline isomers. The positions of the nitro groups in each case were proved by means of NMR and electronic spectra.

Some dinitro derivatives of indoline itself have been described in [1-3]. Similar information on indoline homologs is completely absent.

This communication is devoted to the synthesis of some dinitro derivatives of 2-methylindoline. The latter are of interest, since it is known that the introduction of a methyl group into molecules of physiologically active compounds results in the manifestation by these compounds of an absolutely opposite effect (antimetabolites) [4].

The starting 2-methylindoline was obtained in 85% yield from 2-methylindole by using a somewhat modified method [5] of reduction by zinc in hydrochloric acid. The nitration of 2-methylindoline with nitric acid in an aprotic solvent (acetic anhydride) gave 5-nitro-1-acetyl-2-methylindoline; the nitration of 2-methylindoline with a nitrating mixture gave 6-nitro-2-methylindoline when nitric acid with sp. gr. 1.46 was used instead of nitric acid with sp. gr. 1.52, as in the method in [3]. This made it possible to considerably simplify the nitration due to less resinification and, consequently, gave a purer nitroindoline with an increase in its yield to 98%. A quantitative yield of 6-nitro-1-acetyl-2-methylindoline was obtained by the acylation of 6-nitro-2-methylindoline with acetic anhydride.

The acetyl derivatives of the mononitro isomers were nitrated in an aprotic medium (acetic anhydride) using fuming nitric acid (sp. gr. 1.51). The nitration of 5-nitro-1-acetyl-2-methylindoline gives 5,7-dinitro-1-acetyl-2-methylindoline, while the nitration of the 6-nitro isomer gives a mixture of 5,6- and 6,7-dinitro-1-acetyl-2-methylindolines, which were separated by crystallization and preparative thin-layer chromatography. The acetyl protectors of all of the synthesized dinitro isomers were removed by the usual method by refluxing with hydrochloric acid (1:1).

The positions of the nitro groups in all of the synthesized dinitro isomers were confirmed by means of the NMR spectra. Two doublets with chemical shifts of 6.80 and 7.16 ppm ($J_0 = 6.5$ Hz) are observed in the spectrum of the 6,7-dinitro isomer. The spectrum of the isomeric 5,6-dinitro-2-methylindoline has two singlets with chemical shifts of 7.60 and 6.80 ppm, corresponding to the protons in the 4- and 7-positions, while the spectrum of the 5,7-isomer is characterized by two singlets with chemical shifts of 7.53 and 6.76 ppm, corresponding to the 4-H and 6-H protons.

The compounds with meta and ortho orientations of the nitro groups make it possible to distinguish the electronic spectra. From a comparison of the spectra, it is apparent that the absorption band of the 5,7-dinitro isomer is more intense and shifted to the short-wave region as compared with the spectra of

*See [6] for communication XII.

† Deceased.

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the 5,6- and 6,7-dinitro isomers. A comparison of the absorption spectra of the dinitro isomers and their corresponding acetyl analogs shows that the electron-acceptor effect of the acetyl group leads to a hypsochromic shift of the absorption bands with a corresponding decrease in intensity.

EXPERIMENTAL

2-Methylindoline. A one-third portion of zinc dust [from a total of 70 g (1.1 g-atom)] was added to a solution of 20 g (0.15 mole) of 2-methylindole in 70 ml of butanol, and a total of 550 ml of hydrochloric acid (1:1) was added dropwise. The second portion of zinc dust was introduced after 1 h, while the third portion was introduced after another 1.5 h. At the end of the reaction, the unchanged zinc dust was removed by filtration, and the filtrate was made alkaline with ammonia. The indoline was extracted with three 30-40 ml portions of butanol. The butanol was removed by distillation, and the indoline was vacuum distilled to give 17 g (85%) of a fraction with bp 106° (15 mm) and n_D^{20} 1.5702 (n_D^{20} 1.5719 [5]).

5-Nitro-1-acetyl-2-methylindoline, 5-Nitro-2-methylindoline [1], 6-Nitro-1-acetyl-2-methylindoline, and 6-Nitro-2-methylindoline [3]. These were obtained by known methods. The constants of the synthesized compounds were in agreement with the literature data.

5,7-Dinitro-1-acetyl-2-methylindoline. A total of 2.5 ml of nitric acid with sp. gr. 1.50 was added dropwise with ice cooling to a suspension of 8 g (0.04 mole) of 5-nitro-1-acetyl-2-methylindoline in 15 ml of acetic anhydride. At the end of the addition of the nitric acid, the temperature of the reaction mixture increased sharply and the solid material dissolved and reprecipitated in a short time. The reaction mass was poured into ice water, and the precipitate was washed with water and ether to give 6.8 g (68%) of a product with mp 134° (from toluene). UV spectrum: λ_{\max} , nm (log ϵ): 234 (4.03), 349 (4.00). Found %: C 49.4, 49.4; H 4.4, 4.6. $C_{11}H_{11}N_3O_5$. Calculated %: C 49.9; H 4.2.

5,7-Dinitro-2-methylindoline. A 2 g (0.008 mole) sample of 5,7-dinitro-1-acetyl-2-methylindoline was heated on a boiling-water bath for 1 h with 60 ml of hydrochloric acid (1:1) until the solid dissolved. The mixture was neutralized with concentrated ammonium hydroxide. The dark precipitate was removed by filtration, washed with water, and recrystallized to give 1.2 g (66%) of a mustard-colored powder with mp 161°. UV spectrum: λ_{\max} , nm (log ϵ): 215 (4.02), 264 (3.99), and 390 (4.12). Found %: C 48.2, 48.3; H 4.0, 4.0. $C_9H_9N_3O_4$. Calculated %: C 48.5; H 4.0.

5,6-Dinitro-1-acetyl-2-methylindoline and 6,7-Dinitro-1-acetyl-2-methylindoline. A total of 3 ml (0.03 mole) of concentrated HNO_3 (sp. gr. 1.51) was added dropwise with ice cooling to a suspension of 7 g (0.03 mole) of 6-nitro-1-acetyl-2-methylindoline in 16 ml of acetic anhydride. At the end of the addition, the temperature of the reaction mass rose sharply to 50° and the solid dissolved and subsequently reprecipitated on cooling. The reaction mass was poured into ice water. The light-yellow precipitate was filtered and washed successively with water and ether to give 7.8 g of a mixture of 5,6-dinitro- and 6,7-dinitro-1-acetyl-2-methylindolines. Three recrystallizations from chloroform gave 5 g (58%) of 5,6-dinitro-1-acetyl-2-methylindoline as large, lemon-colored crystals with mp 169-170°. UV spectrum: λ_{\max} , nm (log ϵ): 233 (4.06), 253 (4.06), and 350 (3.93) (chloroform). Found %: C 49.8, 49.8; H 4.2, 4.3. $C_{11}H_{11}N_3O_5$. Calculated %: C 49.9; H 4.2.

A total of 1.8 g (24%) of yellow crystals of 6,7-dinitro-1-acetyl-2-methylindoline with mp 143-145° was isolated from the mother liquor after separation of the 5,6-dinitro-1-acetyl-2-methylindoline by preparative chromatography on aluminum oxide with 13 × 18 cm² plates and elution with chloroform. UV spectrum: λ_{\max} , nm (log ϵ): 230 (4.08) and 346 (3.96). Found %: C 49.5, 49.5; H 4.5, 4.2. $C_{11}H_{11}N_3O_5$. Calculated %: C 49.9; H 4.2.

5,6-Dinitro-2-methylindoline. A 0.5 g (0.002 mole) sample of 5,6-dinitro-1-acetyl-2-methylindoline was heated on a water bath for 1 h with 30 ml of hydrochloric acid (1:1). The resinous residue was filtered, and the ice-cooled filtrate was neutralized with concentrated ammonium hydroxide. The resulting precipitate was filtered and washed with water and a small amount of ether to give 0.3 g (63%) of a product with mp 176° (from alcohol). UV spectrum: λ_{\max} , nm (log ϵ): 231 (4.03), 256 (4.05), 394 (4.04). Found %: C 48.1, 48.2; H 3.9, 4.0. $C_9H_9N_3O_4$. Calculated %: C 48.5; H 4.0.

6,7-Dinitro-2-methylindoline. This compound [0.35 g (76%)] was similarly obtained from 0.5 g (0.002 mole) of 6,7-dinitro-1-acetyl-2-methylindoline as crystals with mp 104-106°. UV spectrum: λ_{\max} , nm (log ϵ): 230 (4.05), 244 (3.96), and 415 (4.14). Found %: C 48.1; 48.3; H 3.9, 4.0. $C_9H_9N_3O_4$. Calculated %: C 48.5; H 4.0.

The course of the reaction and the purity of the compounds obtained were chromatographically monitored by thin-layer chromatography on a loose layer of activity II aluminum oxide (Brockmann system) with a chloroform-saturated ammonium hydroxide system. The UV spectra were obtained with an SF-4A spectrometer.

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