UDC 547.836.7

# THE CHEMISTRY OF INDOLE

## I. Nitration of Lilolidenes

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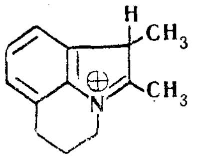
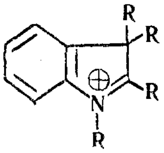
Khimiya Geterotsiklicheskikh Soedinenii, Vol. 2, No. 1, pp. 39-45, 1966

The possibility of an electrophilic substitution reaction in the lilolidene series is shown. It is established that, when 2, 3-dimethyl-1, 7-trimethyleneindole (9, 10-dimethyl-9-lilolidene) is nitrated, the main product is the 5-nitro derivative with some of the 6-nitro isomer. The structure of the compounds obtained is established by the combined use of UV and NMR spectra. The conditions for the dehydrogenation of lilodines to lilolidenes are found. It is shown that the indoline system is dehydrogenated more readily than the tetrahydroquinoline system. The nitro compounds obtained are reduced to the corresponding amines by hydrazine hydrate in the presence of Raney nickel.

We have previously described the synthesis of a number of lilolidenes and benzpyrrolizines from the corresponding 1-aminotetrahydroquinolines or 1-aminoindolines by means of the Fischer reaction [1-7]. The compounds thus obtained are convenient materials for studying the reactions of the indole nucleus, since they usually have substituents in positions 1, 2, 3, and 7, which establishes their stability in acid media and simplifies the analysis of the reaction products.

In the indole series, electrophilic substitution in the pyrrole portion of the molecule has been quite widely studied. There is only a limited number of papers on substitution in the benzene ring, however, and the orientation rules in this case are not yet established. It is known that 5-nitro derivatives are chiefly formed on nitration of indoles in concentrated sulfuric acid [8, 9], sometimes together with some of the 6-nitro compounds [10]. The first step is apparently the attachment of a proton to form an equilibrium mixture of molecules protonated in the 1, 2, or 3 position [11], species with the indolenine structure predominating:





This mixture undergoes attack by the nitronium cation. Here it is not the free electron pair of the hetero atom which is in conjugation with the π-electron system of the benzene ring, as in the case of the anilines, but the π-electrons of the C=N multiple bond. This establishes para orientation by a nitrogen atom in a state of $sp^2$ hybridization, independently of whether the free electron pair on nitrogen is coordinated or not. The indolenines and their salts are therefore nitrated exclusively in position 5 [16]. The formation of small quantities of 6-nitro derivatives can be explained either by instability of the indole cation or by a process in which a species protonated on the nitrogen atom undergoes electrophilic attack.

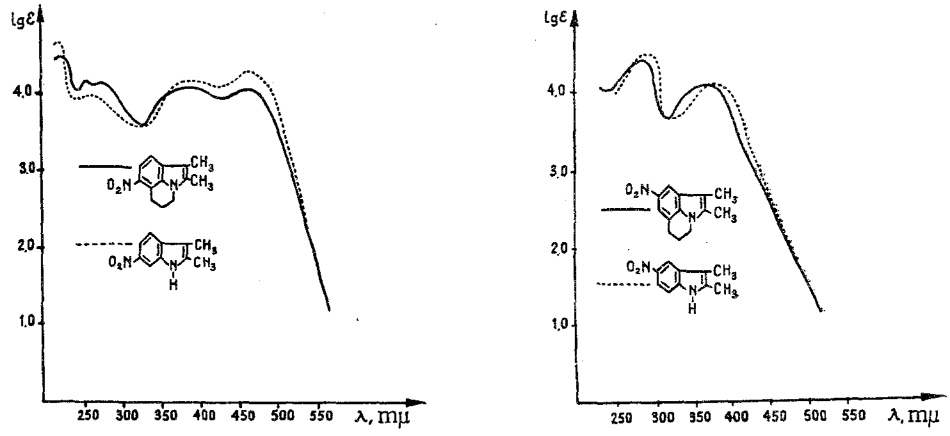
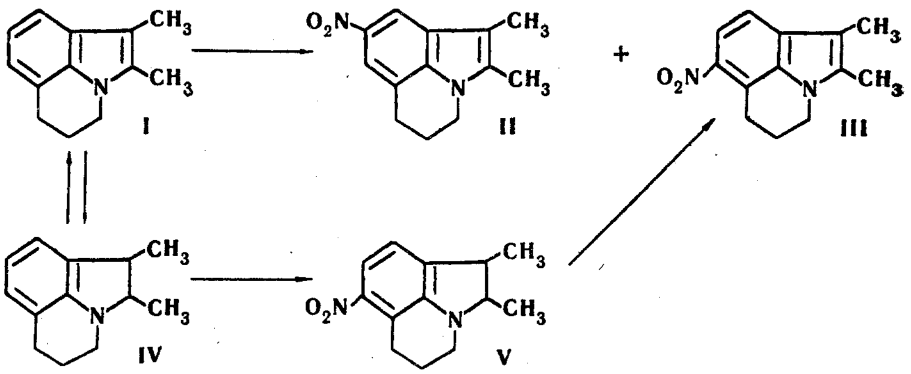


Fig. 1. UV spectra of II, III, and 5- and 6-nitro-2, 3-dimethylindole.

There are data to the effect that 6-nitro derivatives are predominantly obtained on nitration of indolines by a mixture of nitric and sulfuric acids [12].

We have investigated the nitration of 2, 3-dimethyl-1, 7-trimethyleneindole (i.e., 9, 10-dimethyl-9-lilodene). When a nitrating mixture acts on compound I, a mononitro derivative II, mp 167°, is obtained in good yield together with a small quantity of an isomeric mononitro derivative III, mp 120°. The absorption maxima in the UV spectrum of II lie near 285 and 345 mμ, i.e., a bathochromic shift of both maxima is observed in comparison with the starting material ($\lambda_{max}$ 232 and 290 mμ); this is characteristic of 5-nitroindoles in contrast to the 4- and 6-isomers, in which only the long wavelength maximum shifts [13]. A shift of this latter sort takes place with the isomeric nitro compound III.

Reduction of the original dimethyllilolidene I by zinc in hydrochloric acid leads to the corresponding indoline IV. It was established by special experiments that when this substance is dehydrogenated it is not the six-membered, but the five-membered ring which is aromatized, with conversion to the original indole structure I, i.e., the indoline system is dehydrogenated more readily than the tetrahydroquinoline system.

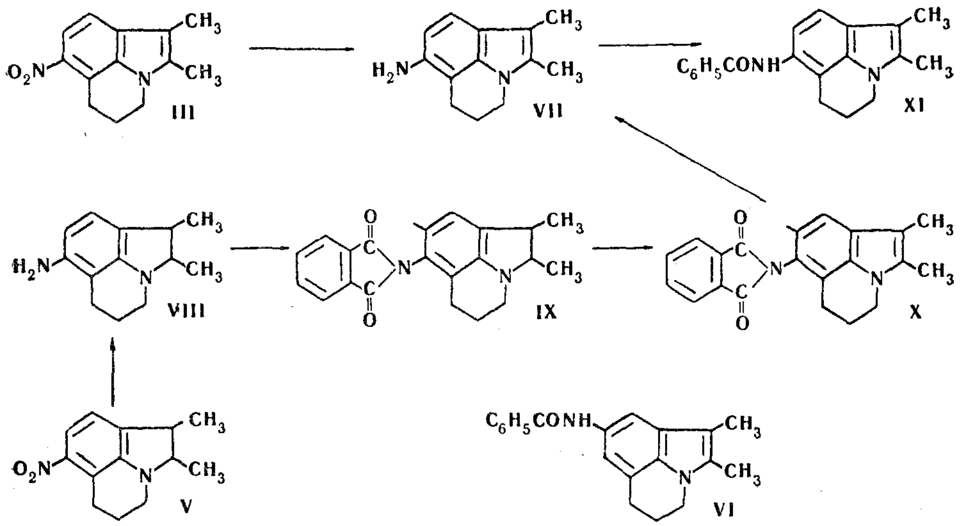


By nitrating 2, 3-dimethyl-1, 7-trimethyleneindoline (IV) in concentrated sulfuric acid, we obtained a mononitro compound V in the form of a noncrystalline oil, which we dehydrogenated without further purification to obtain a nitroindole identical with the substance III formed on nitration of 2, 3-dimethyl-1, 7-trimethyleneindole (I).

By comparing the NMR spectra (Fig. 2) of the original 2, 3-dimethyl-1, 7-trimethyleneindole (I), the nitro isomers II and III, 1, 2, 3, 4, 7-pentamethylindole, and 2, 3, 5-trimethyl-1, 7-trimethyleneindole in $CCl_4$ or $CDCl_3$ (Varian A-60), we succeeded in establishing the positions of the substituents exactly. The peaks with $\tau$ = 7.78-7.82 in the 2, 3-dimethyl-1, 7-trimethyleneindole spectrum are to be assigned to the methyl group protons. The multiplet from the middle methylene group of the trimethylene bridge lies in the same region. The triplet with $\tau$ = 7.07, 7.17, and 7.28 is to be assigned to the methylene group bonded to the benzene ring, and the triplet with $\tau$ = 6.10, 6.19, and 6.29 to the methylene group bonded to the nitrogen atom. The multiplet in the low-field region relates to the three interacting aromatic protons. The spectrum of the 5-nitro derivative is similar to the spectrum of the original substance, except for the aromatic region where, in place of the multiplet, two distinct single peaks with $\tau$ = 1.90 and 2.38 are observed. This confirms that the nitro group is on carbon atom number 5, since we have analogous single peaks in 2, 3, 5-trimethyl-1, 7-trimethyleneindole, whose structure is known. In the spectrum of the second nitro isomer, a quadruplet with a splitting constant of 7.5 cps is observed in the aromatic proton region; this is characteristic of two interacting ortho protons. The possibility of anomalous nitration on the methyl groups of the pyrrole ring or on the methylene groups of the six-membered ring and the addition of nitric acid to the 2, 3 double bond are excluded by a comparative examination of all the spectra. In the case of the 5-nitro derivative, approximately equal shifts are observed for the triplets from the methylene groups bonded to the benzene ring and to the nitrogen atom, while in the second nitro isomer a larger shift is observed for the triplet from the methylene group bonded to the benzene ring. Such a shift, of ~ 0.5 ppm, can be explained only by the effect of a nitro group located close by. Actually, it is known that, in the nitrotoluenes, the corresponding shifts of the methyl group protons o, m, and p to the nitro group equal 0.23, 0.07, and 0.08, respectively [14]. Thus the nitro group in compound III is in position 6. The authors are grateful to Prof. R. Woodward (Harvard University, USA) for his help in interpreting the NMR spectra.

The nitro compounds were reduced to the corresponding amines by hydrazine hydrate in the presence of Raney nickel. Because of its very ready oxidizability, 5-amino-2, 3-dimethyl-1, 7-trimethyleneindole was isolated only in the form of its benzoyl derivative VI. The corresponding 6-aminoindole (VII) and 6-aminoindoline (VIII) are more stable and were obtained in the free state. We succeeded in dehydrogenating 6-amino-2, 3-dimethyl-1, 7-trimethyleneindoline after protecting the amino group by a phthalyl residue according to the procedure described for 6-amino-1-methylindoline [15]. After removal of the phthalyl protecting group and Schotten-Baumann benzoylation, we arrived at

6-benzamido-2, 3-dimethyl-1, 7-trimethyleneindole, which is also obtained from 6-nitro-2, 3-dimethyl-1, 7-trimethyleneindole after reduction and benzoylation.



## Experimental

Dehydrogenation of 2, 3-dimethyl-1, 7-trimethyleneindoline (9, 10-dimethyllilolidine) (IV). A mixture of 9.5 g 9, 10-dimethyllilolidine [3], 12.5 g chloranil, and 200 ml xylene was boiled for 18 hr. The xylene solution was washed successively with alkali, water, dilute hydrochloric acid, and again with water. The xylene was distilled off in vacuo and 6 g (63%) IV, mp 87° (from alcohol), was obtained [3]. A mixed sample with known 9, 10-dimethyl-9-lilolidene gave no depression.

Nitration of 2, 3-dimethyl-1, 7-trimethyleneindole. To a solution of 15 g I in 150 ml concentrated sulfuric acid

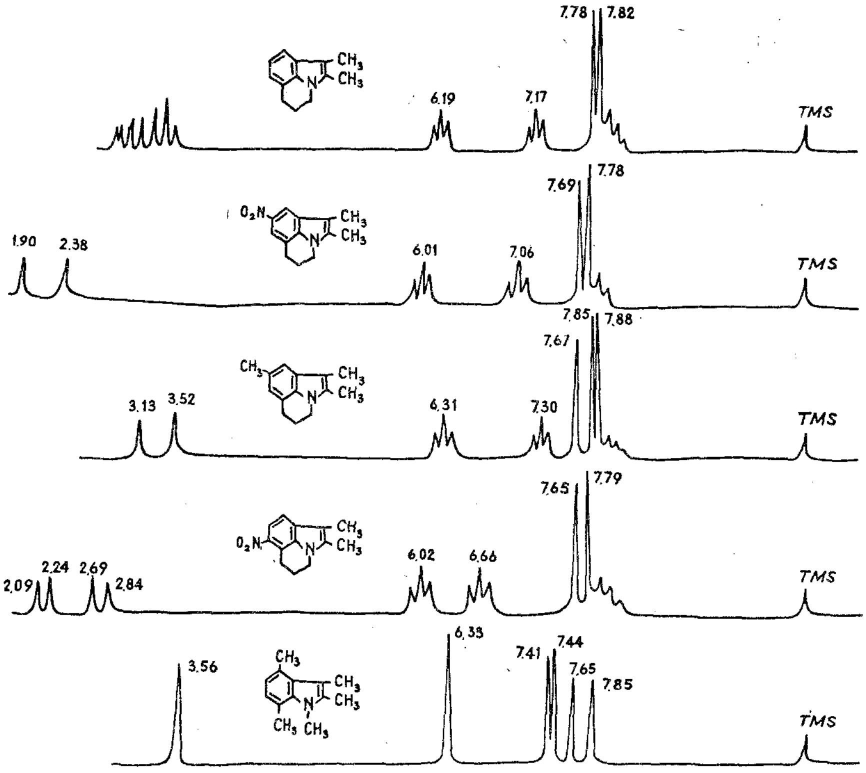


Fig. 2. NMR spectra of I, II, 2, 3, 5-trimethyl-1, 7-trimethyleneindole, III, and 1, 2, 3, 4, 7-pentamethylindole.

cooled to −8° was added 5.5 g nitric acid (d 1.5) mixed with 25 ml sulfuric acid. After the addition, the reaction mixture was stirred for 1 hr (the temperature being gradually raised to 0°) and poured onto ice. The precipitate was filtered, washed with water, and dried in air. Yield 16.5 g (90%). After crystallization from alcohol, 5-nitro-2, 3-dimethyl-1, 7-trimethyleneindole, mp 167°, was obtained. Found: C 67.86, 68.04; H 6.22, 6.27; N 11.93, 12.07%. Calculated for $C_{13}H_{14}N_2O_2$: C 67.82; H 6.09; N 12.17%.

From the mother liquors there was isolated 200 mg 6-nitro-2, 3 dimethyl-1, 7-trimethyleneindole, mp 120° (from alcohol). Found: C 67.82, 67.91; H 6.21, 6.26; N 11.84, 12.00%. Calculated for $C_{13}H_{14}N_2O_2$: C 67.82; H 6.09; N 12.17%.

6-Nitro-2, 3-dimethyl-1, 7-trimethyleneindole (III). To a solution of 5.5 g 2, 3-dimethyl-1, 71 trimethyleneindoline in 40 ml concentrated sulfuric acid cooled to −3° was added 2.5 g nitric acid (d 1.5) mixed with 15 ml concentrated sulfuric acid. After addition of all the nitrating mixture (1.5 to 2 hr), the reaction mixture was stirred 45 min more at + 2°, poured onto ice, made basic with sodium carbonate, and extracted with ether. After distillation of the ether, there was obtained 7 g (quantitative yield) of a reddish oil, which was boiled for 20 hr with 7.5 g chloranil and 120 ml xylene. The xylene solution was treated with alkali, then with water, dilute hydrochloric acid (1:1), and again with water. The xylene was distilled off in vacuum and 4 g (54%) III, mp 120° (from alcohol), was obtained. A mixed sample with 6-nitro-2, 3-dimethyl-1, 7-trimethyleneindole obtained by nitrating 2, 3-dimethyl-1, 7-trimethyleneindole gave no depression.

5-Benzamido-2, 3-dimethyl-1, 7-trimethyleneindole (VI). To a solution of 3 g 5-nitro-2, 3-dimethyl-1, 7-trimethyleneindole in 50 ml methyl alcohol was added a little Raney nickel and twice the quantity of hydrazine hydrate (dropwise). The reaction proceeded with evolution of heat. After addition of all the hydrazine hydrate (2 hr), the reaction mixture was boiled for 2 hr. The alcohol and excess hydrazine hydrate were distilled off in vacuum, the residue was dissolved in benzene, and a dilute solution of base and several drops of benzoyl chloride were added. The mixture was carefully shaken until the odor of benzoyl chloride disappeared, and the precipitate was separated. There was obtained 2.6 g (80%) VI, mp 167° (from benzene). Found: N 9.12, 9.26%; Calculated for $C_{20}H_{20}N_2O$: N 9.20%.

6-Amino-2, 3-dimethyl-1, 7-trimethyleneindole (VII) was obtained from the corresponding nitro derivative by the procedure given for the 5-aminoindole VI; yield 93%, mp 80-81°, bp 219° (16 mm). Found: N 13.95, 14.14%. Calculated for $C_{13}H_{16}N_2$: N 13.96%.

The benzoyl derivative, mp 221° (from benzene), was obtained by Schotten-Baumann benzoylation. Found: N 8.95, 9.11%. Calculated for $C_{20}H_{20}N_2O$: N 9.20%.

6-Amino-2, 3-dimethyl-1, 7-trimethyleneindoline (VIII). The oil (2.5 g) obtained after nitration of 2, 3-dimethyl-1, 7-trimethyleneindoline was dissolved in alcohol and a little Raney nickel and 8 ml hydrazine hydrate were added (dropwise). After addition of all the hydrazine hydrate (30 min), the reaction mixture was boiled 3 hr. After fractional distillation in vacuum, the yield was 2 g (90%) VIII, bp 182-184° (16 mm). The benzoyl derivative, mp 159° (from benzene), was obtained by Schotten-Baumann benzoylation. Found: N 9.11, 9.28%. Calculated for $C_{20}H_{22}N_2O$: N 9.14%.

6-Phthalimido-2, 3-dimethyl-1, 7-trimethyleneindoline (IX). A mixture of equimolar quantities of VIII and phthalic anhydride, carefully ground in a mortar, was heated to 160° in a porcelain dish. The desired substance IX, mp 173-174° (from alcohol), was obtained after crystallization from alcohol. Found: N 8.23, 8.31%. Calculated for $C_{21}H_{20}N_2O_2$: N 8.48%.

6-Phthalimido-2, 3-dimethyl-1, 7-trimethyleneindole (X). A mixture of 3.3 g IX, 2.5 g chloranil, and 60 ml xylene was refluxed for 8 hr. The xylene solution was washed with alkali, filtered, and washed successively with water, dilute hydrochloric aic, and again with water. The xylene was distilled off in vacuum and 2.5 g (78%) X, mp 233-234° (from alcohol), was obtained. Found: N 8.78, 8.80%. Calculated for $C_{21}H_{18}N_2O_2$: N 8.59%.

6, Benzamido-2, 3-dimethyl-1, 7-trimethyleneindole (XI). To 1.5 g X in 40 ml alcohol was added 1 ml hydrazine hydrate, the mixture was boiled 2 hr and cooled, the phthalazine that separated was filtered off, the alcohol was evaporated, and the residue was dissolved in benzene. To the benzene solution were added 40 ml dilute alkali and several drops of benzoyl chloride, the mixture was carefully shaken, and the precipitate was separated. There was obtained 1.1 g (80%) XI, mp 221° (from benzene). Found: N 9.12, 9.26%. Calculated for $C_{20}H_{20}N_2O$: N 9.20%.

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30 October 1964

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