# SUBSTITUTED 2-METHYL- AND 2-METHYLENEINDOLINES.

## 3.* NITROAMINO-5,6-DISUBSTITUTED 2-METHYL- AND 2-METHYLENEINDOLINES

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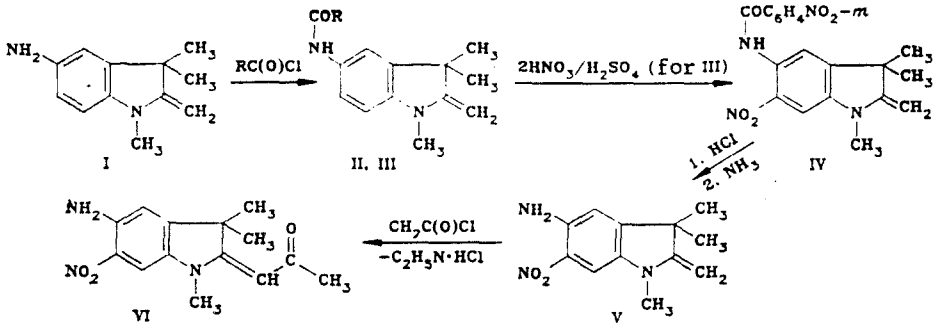
UDC 547.754.07: 542.422.25

*A method is developed for the synthesis of 5,6-disubstituted nitroamino- and nitromethylamino-2-methyl- and -2-methyleneindolines. These are starting compounds for the synthesis of 2-methyleneindolines condensed with some heterocycle.*

1,3,3-Trimethyl-2-methyleneindoline (Fischer's base) and its quaternary salts are the starting materials for the synthesis of dyes [2-5]. The present report is devoted to the synthesis of 5,6-disubstituted 2-methyl- and 2-methyleneindolines with nitro, amino, and methylamino groups. These compounds can be used to prepare 2-methyleneindolines condensed with other heterocycles.

From 1,3,3-trimethyl-2-methylene-5-aminoindoline (I), 5-acetylamino- and 5-benzoylaminoindolines (II and III) are prepared by the usual procedure [1]. On the nitration of benzoyl derivative III with an excess of nitrating mixture [6], dinitro derivative IV is formed. Nitration with 1 mole of nitric acid leads to the formation of a mixture of products since both the benzoyl group and the benzene ring of the heterocycle are nitrated (according to the PMR spectrum). Acylation of indoline V, obtained after hydrolysis, with acetyl chloride occurs solely at the methylene carbon atom in view of the strong reduction of the nucleophilicity of the amino group.




Nitration of acetylaminoindoline II as well as of 5- and 6-N-acetylamino-1,2,3,3-tetramethyleneindolines leads to the formation of mixtures of oxidized indolines.

It was recently shown [7] that a mixture of 5- and 6-substituted indolines VIII is obtained by the amidomethylation of Fischer's base VII with N-hydroxymethylphthalimide in concentrated $H_2SO_4$ in a Chernyaka–Ainkhorn reaction. From this, the authors of [7] isolated only the 5-isomer, which is the major product. We nitrated the mixture of isomers without separating them from the reaction medium. In this case, both isomers were formed, indoline IX in high yield and indoline X in very insignificant yield.

*See [1] for Communication 2.

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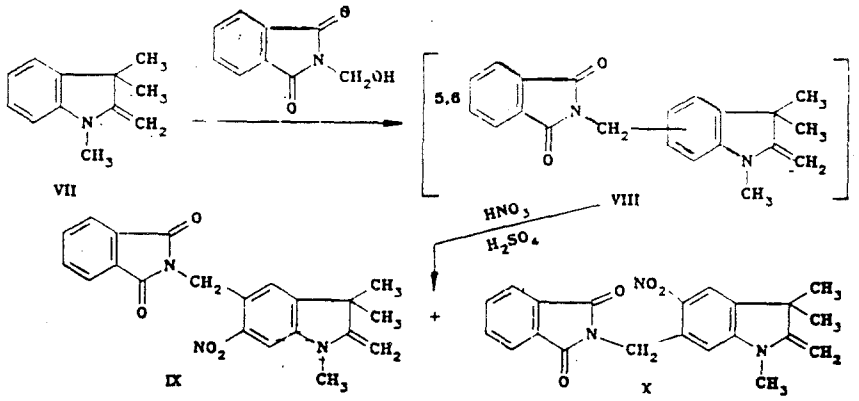
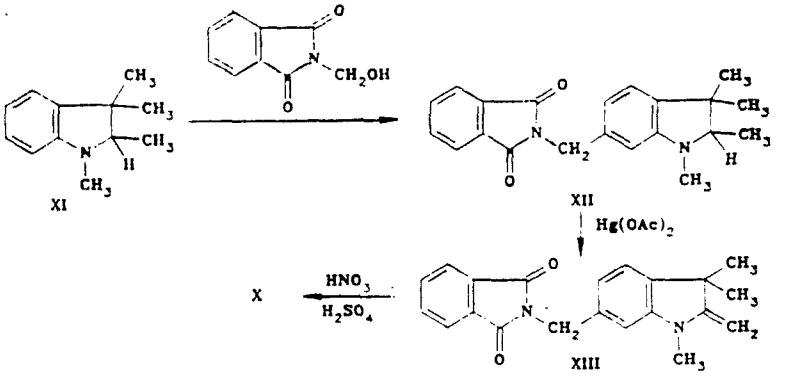
TABLE 1. Characteristics of Compounds II-VI, IX, X, and XII-XV

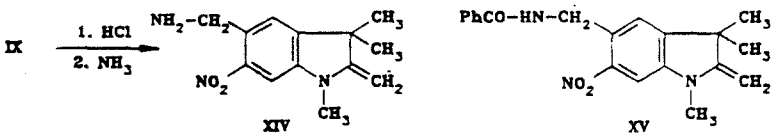
| Compound | Empirical formula | mp, °C | IR spectrum, $cm^{-1}$ | PMR spectrum, ppm (SSCC, J, Hz) | | | | | | | | Yield, % |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | N—$CH_3$ | 2-H | 3-$CH_3$ | 4-H | 5-H | 6-H | 7-H | remaining protons | |
| II | $C_{14}H_{18}N_2O$ | 123...124 | 1655 (CO); 3290 (NH); 1625 (=CH) | 3,00 | 3,82 | 1,30 | 7,28 ($J_{46}$=2,0) | — | 7,16 ($J_{67}$=8,0; | 6,43 | 7,58 (NH); 2,12 (OC—$CH_3$) | 86 |
| III | $C_{19}H_{20}N_2O$ | 205...206 | 1650 (CO); 3290 (NH); 1610 (=CH) | 3,03 | 3,85 | 1,35 | — | — | 7,29 ($J_{67}$=8,0) $J_{64}$=2,0) | 6,48 | 7,91...7,44 (Ar—H, 4-H) | 74 |
| IV | $C_{19}H_{18}N_4O_5$ | 162...164 | 1650 (CO); 3340 (NH); 1505, 1345 ($NO_2$); 1600 (=CH) | 3,11 | 4,00 | 1,44 | 8,67 | — | — | 7,30 | 11,48 (NH); 8,88 (2′-H); 7,75 (4′-H); 7,75 (5′-H); 8,28 (6′-H) | 68 |
| V | $C_{12}H_{15}N_3O_2$ | 94 | 1500, 1320 ($NO_2$); 3510, 3380 ($NH_2$); 1600 (=CH) | 3,02 | 3,84 | 1,33 | 6,56 | — | — | 7,08 | 6,05 ($NH_2$) | 64 |
| VI | $C_{14}H_{17}N_3O_3$ | 224...225 | 1620 (CO); 3480, 3370 ($NH_2$); 1510, 1320 ($NO_2$); 1600 (=CH) | 3,18 | (5,31) | 1,70 | 6,71 | — | — | 7,37 | 6,44 ($NH_2$); 2,19 ($OCCH_3$) | 71 |
| IX | $C_{21}H_{19}N_3O_4$ | 181...182 | 1720 (CO); 1525, 1340 ($NO_2$); 1620 (=CH); 1650 ($=CH_2$) | 3,6 | 3,94 | 1,27 | 6,96 | — | — | 7,09 | 5,18 (5-$CH_2$); 7,93...7,69 (Ar—H) | 53 |
| X | $C_{21}H_{19}N_3O_4$ | 202...203 | 1720 (CO); 1525, 1310 ($NO_2$); 1620 (=CH) | 2,94 | 4,08 | 1,32 | 7,96 | — | — | 6,15 | 5,36 (6-$CH_2$); 7,98...7,74 (Ar—H) | 79 |
| XII | $C_{21}H_{22}N_2O_2$ | 148...149 | 1720 (CO); 1600 (=CH) | 2,68 | 2,86 q ($J$=6,6); 1,14 d ($CH_3$, $J$=6,6) | 0,96; 1,23 | 6,98 ($J_{45}$=8,0) | 6,79 ($J_{57}$=1,5) | — | 6,58 | 4,77 (6-$CH_2$); 7,87...7,62 (Ar—H) | 63 |
| XIII | $C_{21}H_{20}N_2O_2$ | 150...151 | 1720 (C=O); 1610 (=CH) | 3,01 | 3,81 | 1,29 | 7,00 ($J_{45}$=7,0) | 6,83 ($J_{57}$=1,5) | — | 6,62 | 4,97 (6-$CH_2$); 7,90...7,64 (Ar—H) | 67 |
| XIV | $C_{13}H_{17}N_3O_2$ | 92...93 | 2970 (NH); 1510, 1350 ($NO_2$); 1620 (=CH) | 3,08 | 3,98 | 1,37 | 7,09 | — | — | 7,18 | 1,83 ($NH_2$); 3,96 (5-$CH_2$) | 59 |
| XV | $C_{20}H_{21}N_3O_3$ | 85...86 | 1640 (CO); 3300 (NH); 1510, 1330 ($NO_2$); 1610 (=CH) | 3,07 | 3,98 | 1,36 | — | — | — | 7,13 | 4,73 (5-$CH_2$); 7,81...7,36 (Ar—H, 4-H) | 65 |



To prepare compound X, we chose a different route. The amidomethylation of tetramethylindoline XI under the conditions described above leads to the formation of a single compound XII, in contrast to the amidomethylation of dialkylanilines [8]. The location of the introduced substituent is shown unambiguously by the PMR spectra. 2-Methyleneindoline XIII is obtained from the oxidation of tetramethylindoline XII by the method proposed by us earlier [9]. Nitration of XIII allowed indoline X to be isolated as the sole product in good yield. At the same time, when tetramethylindoline XII is nitrated, a mixture of products is formed in which 2-methyleneindolines are present (according to the PMR spectra and the qualitative reaction with p-dimethylamino benzaldehyde).



The transition from the nitroindoline with an amidomethyl group, IX, to a nitroindoline with an aminomethyl group, XIV, and its benzoyl derivative, XV, is brought about in the usual way.



In the PMR spectra (Table 1) of all the 5-monosubstituted indolines, the signal from the proton in the 7 position is located at quite a high field (6.4-6.7 ppm) and appears as a doublet with $J_o$ = 7-8 Hz. For the 6-monosubstituted indolines, the signal from the proton in the same position appears as a doublet with $J_m$ = 1.5-2 Hz. The spectra of similar indolines are described in papers [1, 8-10]. It is of interest to note that, in compound XV, the two protons of the aliphatic $CH_2$ group appear as a doublet because of splitting by the neighboring NH group. On homodecoupling at the NH group frequency, the signal from the $CH_2$ group degenerates to a singlet.

When the spectra of compound XIV are taken with the LSR [lanthanide shift reagent] $Eu(FOD)_3$, the signal with a chemical shift of 1.8 ppm is the most strongly shifted. This gives grounds for asserting that this signal corresponds to the $NH_2$ group through which molecules XIV is coordinated to the LAR. The peak at 3.97 ppm is split in the presence of $Eu(FOD)_3$ into two signals differing considerably in the values of the induced shifts, with an integral intensity of 2H each. The signal that is most strongly shifted corresponds to the $CH_2$–N group, and the other to a proton of the exocyclic methylene group. On the addition of a considerable excess of LSR, this signal is split into a doublet of doublets with $^2J$ = 1 Hz.

. Syntheses of the heterocondensed indolines based on the compounds obtained will be described later.

## EXPERIMENTAL

The IR spectra were taken on a UR-20 instrument in KBr tablets. The PMR spectra were taken on a Bruker WP-100SY spectrometer in $CDCl_3$ with TMS as an internal standard.

The elementary analyses of the compounds corresponded to the calculated values.

**1,3,3-Trimethyl-2-methylene-5-acetylaminoindoline (II).** A solution of 5 mmoles of acetyl chloride in 10 ml of benzene is added to a solution of 5 mmoles of 1,3,3-trimethyl-2-methylene-5-aminoindoline (I) in 15 ml of benzene and 6 ml of triethylamine cooled to –5°C. The mixture is held at 20°C for 24 h, the triethylamine hydrochloride filtered off, the benzene evaporated off under vacuum, and the residue triturated with heptane. The analytical sample was recrystallized from heptane.

**1,3,3-Trimethyl-2-methylene-5-benzoylaminoindoline (III).** Eleven mmoles of triethylamine is added to a suspension of 5 mmoles of aminoindoline I in 15 ml of methylene chloride. Five mmoles of benzoyl chloride is added to the greenish solution that forms on cooling to 0°C and the mixture is kept at 20°C for 24 h. The precipitate forming is filtered off, the filtrate washed with water, dried with $Na_2SO_4$, and, after evaporation, the major part of the product is isolated. The analytical sample was recrystallized from dichloroethane.

**1,3,3-Trimethyl-2-methylene-5-nitrobenzoylamino-6-nitroindoline (IV).** Sixty-one mmoles of $HNO_3$ (d = 1.52) in 10 ml of concentrated $H_2SO_4$ is added to a solution of 30 mmoles of indoline III in 40 ml of concentrated $H_2SO_4$ after cooling to –5°C. The temperature is raised to 20°C and held for 2 days. The reaction mixture is poured onto ice and water, neutralized with ammonia, and the precipitate formed is filtered off. Recrystallization is from benzene. The analytical sample was additionally crystallized from heptane.

**1,3,3-Trimethyl-2-methylene-5-amino-6-nitroindoline (V).** Five mmoles of indoline IV in concentrated HCl is boiled for 2 h. The crystals of m-nitrobenzoic acid that form are filtered off, and the filtrate neutralized, with cooling, with 25% aqueous ammonia. The precipitate formed is dissolved in 100 ml of benzene, washed with water, dried with $Na_2SO_4$, and, after evaporation to a volume of 50 ml, precipitated with 200 ml of petroleum ether. The analytical sample was recrystallized from heptane.

**1,3,3-Trimethyl-2-acetylmethyleneindoline (VI)** is prepared analogously to compound II. It is recrystallized from benzene.

**1,3,3-Trimethyl-2-methylene-5-phthalimidomethyl-6-nitroindoline (IX).** Two hundred mmoles of powdered N-methylhydroxyphthalimide is added in small portions with stirring over the course of 45 min at 20°C to a solution of 200 mmoles of indoline VII in 180 ml of concentrated $H_2SO_4$. After complete dissolution, the reaction mixture is kept at 20°C for 70 h. A solution of 200 mmoles of $HNO_3$ (d = 1.52) in 100 ml of concentrated $H_2SO_4$ is added over the course of 1 h at 0°C with vigorous stirring. The mixture is kept for 1 day at room temperature, poured onto 700 g of ice, and neutralized with ammonia. The precipitate formed is filtered off, washed with ammonia and water, and boiled (2 × 100 ml) with acetone. The insoluble, orange powder is pure indoline IX. The analytical sample was recrystallized from benzene.

After evaporation of the acetone, indoline X was isolated in 5% yield by fractional recrystallization from octane.

**1,2,3,3-Tetramethyl-6-phthalimidomethylindoline (XII).** The amidomethylation of indoline XI is carried out analogously to the amidomethylation of indoline VIII. It is purified by boiling with a small amount of acetone. The analytical sample was recrystallized from heptane.

**1,3,3-Trimethyl-2-methylene-6-phthalimidomethyleneindoline (XIII).** A boiling solution of 100 mmoles of mercuric acetate in 100 ml of water is added to a boiling solution of 5 mmoles of indoline XII in 100 ml of glacial acetic acid. The resultant mixture is boiled for 15 min, then cooled. The precipitate of mercurous acetate is filtered off, and an excess of $Na_2SO_4$ is added. The mercuric sulfide precipitate that forms is separated by centrifugation. The reaction mixture is evaporated to a volume of 75 ml and neutralized with ammonia. The product is extracted with chloroform. The analytical sample was recrystallized from heptane.

**1,3,3-Trimethyl-2-methylene-5-nitro-6-phthalimidomethylindoline (X).** Twenty mmoles of $HNO_3$ (d = 1.52) in 5 ml of concentrated $H_2SO_4$ is added at 0°C to a solution of 200 mmoles of indoline XIII in 100 ml of concentrated $H_2SO_4$. The mixture is held for 12 h at 20°C, poured onto ice, and neutralized with ammonia. The analytical sample was recrystallized from heptane.

**1,3,3-Trimethyl-2-methylene-5-aminomethyl-6-nitroindoline (XIV).** Twenty mmoles of indoline IX in 100 ml of concentrated HCl is boiled for 12 h. The precipitated phthalic acid is filtered off after cooling. The product is isolated analogously to indoline V.

**1,3,3-Trimethyl-2-methylene-5-benzoylaminomethyl-6-nitroindoline (XV).** Benzoylation of indoline XIV is carried out analogously to the acylation of indoline I. The product is purified by reprecipitation from benzene with petroleum ether.

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# SYNTHESIS OF 1-β-D-RIBOPYRANOSYL- AND RIBOFURANOSYL-6-NITROINDOLE AND INDOLINE FOR THE PHOSPHOTRIESTER OLIGONUCLEOTIDE SYNTHESIS


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UDC 547.754'455.522



*The glycosylation reaction of 6-nitroindoline with 5-tritylribose led to the synthesis of the 1-β-D-ribofuranoside and 1-β-D-ribopyranoside of 6-nitroindoline, the dehydrogenation of which resulted in the isolation of the corresponding 1-β-D-ribopyranoside and 1-β-D-ribofuranoside of 6-nitroindole; the last with protecting groups are suitable for utilization in oligonucleotide synthesis.*


The modification of natural nucleosides at the heterocyclic base or the carbohydrate residue and the synthesis of nucleosides by the glycosylation of various heterocycles give rise to nucleosides which are not naturally occurring and possess a broad spectrum of biological properties.

The chemical conversions of the monomeric artificial nucleosides in the metabolic cellular stock have been studied in detail. Less is known about their properties in the composition of the polynucleotide chain of RNA or DNA, and the character of the structural and functional changes in the nucleic acids containing artificial analogs of the nucleosides [1-7].


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Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 11, pp. 1500-1506, November, 1990. Original article submitted April 14, 1989.