PORPHYRINS. 13.* REACTION OF meso-DIMETHYLAMINOMETHYLETIOPORPHYRIN I WITH NUCLEOPHILES IN THE PRESENCE OF ZINC ACETATE

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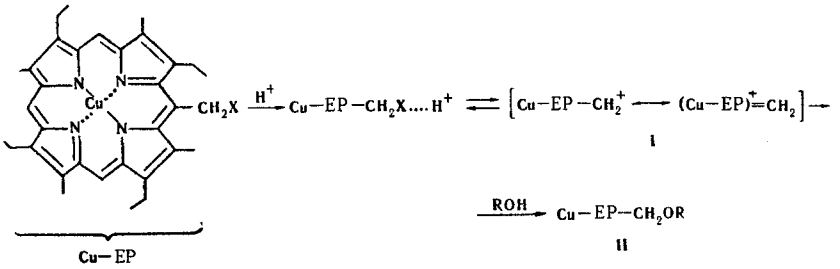
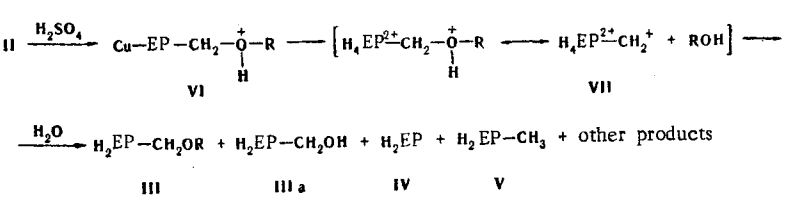
When meso-dimethylaminomethyletioporphyrin I (I) is heated in CCl_4 or tetrahydrofuran (THF) in the presence of zinc acetate, it reacts with alcohols to give the corresponding meso-alkoxymethylporphyrins. Under similar conditions CH acids (acetone, acetylacetone, nitromethane, and others) form the corresponding meso-substituted derivatives with the formation of a C–C bond. Ethers are formed when the copper and nickel complexes of I are heated in ethylene glycol.

We have demonstrated [2] that protonation of copper complexes of etioporphyrin I that contain a CH_2X group (X = OH, OR, or NRR'; R and R' = H or alkyl) in the meso position give stabilized carbonium ions of the benzyl type (I), a characteristic feature of which is the presence of intense bands in the electronic spectrum at 460 and 1020 nm. They react readily with alcohols to give the corresponding copper complexes of ethers of the II type via the scheme



The demetallation of complexes II to free porphyrins III by means of concentrated sulfuric acid, which is the procedure normally used for meso-unsubstituted porphyrins, is inefficient because of the low yields of porphyrins III and the formation of a considerable amount of meso-hydroxymethyletioporphyrin (IIIa), as well as a certain amount of etioporphyrin I (IV), meso-methyletioporphyrin (V), and other porphyrins with unestablished structures. This ambiguous action of sulfuric acid is due to the formation, in the initial instant of the process, of oxonium ion VI, which is subsequently destabilized by demetallation and additional protonation of the carbonium ion (VII):



We confirmed the formation of carbonium ions of the VII type when meso-alkoxymethylporphyrins are dissolved in concentrated sulfuric acid by means of spectral and calculated data [3]. However, the stability

*See [1] for Communication 12.

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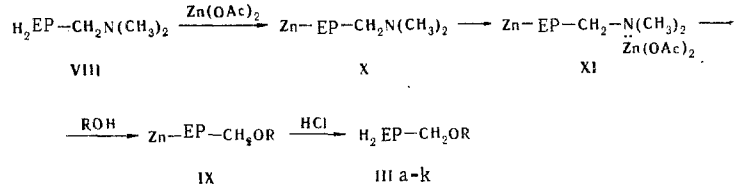
of ion VII is considerably lower than that of ions of the I type.

To obtain the free alkoxymethylporphyrin bases III one must consequently start from a complex of meso-dimethylaminomethyletioporphyrin I that, first, will react readily with an OR^- nucleophile and, second, will not undergo protonation at the meso substituent.

We have observed [4] that porphyrin VIII reacts readily with aliphatic alcohols in anhydrous tetrahydrofuran (THF), carbon tetrachloride, and destabilized freshly distilled chloroform in the presence of zinc acetate to give the corresponding zinc complexes of meso-alkoxymethyletioporphyrin I (IX), from which free porphyrins III can be isolated in high yields (90-95%) by treatment with dilute hydrochloric acid.

We established that zinc complex X is formed in the first instant of the process; however, it reacts with alcohols only in the presence of excess zinc acetate. Consequently, the next step in this reaction is evidently activation of the meso substituent due to bonding of the dimethylaminomethyl group with the formation of intermediate complex XI, which also reacts with alcohols via the scheme



III a R=H; b R=Me; c R=Et; d R=*n*-Pr; e R=*n*-Bu; f R=*t*-Bu; g R=$(CH_2)_2OH$; h R=$(CH_2)_2OMe$; i R=$(CH_2)_6OH$; j R=Ph; k R=CH_2—CH=CH_2

In the series of lower aliphatic alcohols the rate of formation of meso-alkoxymethylporphyrins decreases as the number of methylene links in the alcohol increases. However, steric factors also take on great significance. Thus, for example, the following dependence was observed for butanols: BuOH > sec-BuOH > tert-BuOH. The presence of even small amounts of water is sure to lead to the formation of meso-hydroxymethylporphyrin IIIa.

Of course, one can obtain ethers not only with aliphatic alcohols but also with a large number of other compounds that contain a hydroxy group. The reaction with phenol and 2,4-dimethylphenol, as well as with benzyl alcohol, proceeds very readily and gives the products in virtually quantitative yields. The formation of an ether bond only at one hydroxy group occurs in the presence of a large excess of ethylene glycol, diethylene glycol, and triethylene glycol. The covalent addition of porphyrin to polyethylene glycols with different molecular weights for the creation of colored reagents is also possible.

Of particular interest are ethers with unsaturated alcohols, which may serve as intermediates for subsequent chemical transformations. We obtained either IIIk in 50% yield by the reaction of porphyrin VIII with allyl alcohol. The relatively low yield of the latter is associated with the presence in the reaction mixture of a large amount of side products, which were evidently formed in the reaction of complex XI at the double bond of the allyl alcohol.

All of the meso-alkoxymethylporphyrins that we obtained have very similar electronic spectra of the etio type, regardless of the structure of the alcohol used in the reaction, and this constitutes evidence for the absence of a strong electronic interaction between the porphyrin ring and R through the CH_2—O group.

An intense characteristic band at 1150 cm^{-1}, which corresponds to the ν_{C-O} band of an ether group, is present in the IR spectra.

The presence of molecular-ion peaks, as well as peaks of ions with m/e 507, 492, 491, and 478, which correspond to $(M - R)^+$ (a), $(M - OR + H)^+$ (b), $(M - OR)^+$ (c), and $(M - CH_2OR + H)^{+\cdot}$ (d) fragments, is characteristic for the mass spectra of virtually all of the ethers obtained. The M^+ peaks have the maximum intensities in the mass spectra of the porphyrins with lower alkoxy groups, and the peak of the c ion has the next highest intensity. The intensity of the a ion does not exceed 5-15%, which is completely natural, since cleavage of the C—O band with the formation of stable cation c is more likely. The presence in the mass spectra of intense peaks of b and d ions, particularly in the spectra of complex nonvolatile ethers, is explained by the development of meso-methyletioporphyrin I and etioporphyrin I, respectively, as a result of thermal decomposition of the porphyrins in the ion source of the mass spectrometer.

In the case of a large number of the synthesized porphyrins, which were obtained by the method that we

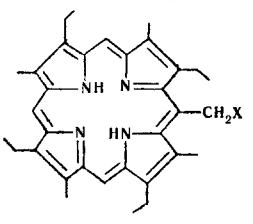
TABLE 1. Mass Spectra of the Compounds Obtained

Compound	Empirical formula	Yield, %	m/e (relative intensity, %)
IIIa	$C_{33}H_{40}N_4O$	68	508 (*M*, 100), 507 (4), 492 (31), 491 (10), 490 (6), 579 (20), 577 (12)
IIIb	$C_{34}H_{42}N_4O$	84	522 (*M*, 100), 507 (4), 492 (23), 491 (28), 490 (6)
IIIc	$C_{35}H_{44}N_4O$	92	536 (*M*, 100), 507 (3), 492 (55), 491 (70), 490 (8), 477 (21), 461 (15)
IIId	$C_{36}H_{46}N_4O$	90	550 (*M*, 100), 507 (5), 492 (42), 491 (68), 490 (10), 479 (65), 478 (90)
IIIe	$C_{37}H_{48}N_4O$	85	564 (*M*, 85), 507 (4), 492 (63), 491 (70), 490 (13), 479 (47), 478 (100)
IIIf	$C_{37}H_{48}N_4O$	32	564 (*M*, 100), 507 (9), 492 (60), 491 (66), 479 (80), 478 (25)
IIIg	$C_{35}H_{44}N_4O_2$	60	552 (*M*, 82), 507 (9), 492 (100), 491 (75), 490 (12), 478 (36)
IIIh	$C_{35}H_{46}N_4O_2$	74	566 (*M*, 100), 536 (5), 507 (12), 492 (65), 491 (76), 490 (13), 478 (24)
IIIi	$C_{39}H_{52}N_4O_2$	75	608 (*M*, 41), 507 (4), 492 (52), 491 (22), 490 (6), 478 (100), 463 (20)
IIIj	$C_{39}H_{44}N_4O$	82	584 (*M*, 20), 582 (5), 492 (100), 478 (58), 463 (14)
IIIk	$C_{36}H_{44}N_4O$	50	548 (*M*, 100), 507 (3), 492 (47), 491 (47), 478 (19)
XIIa	$C_{36}H_{44}N_4O$	35	548 (*M*, 100), 505 (25), 491 (93), 478 (24), 476 (21), 461 (23)
XIIb	$C_{36}H_{39}D_5N_4O$	—	553 (*M*, 90), 507 (20), 491 (100), 477 (25), 462 (23)
XIIc	$C_{38}H_{46}N_4O_2$	85	590 (*M*, 100), 547 (10), 491 (100), 478 (8), 476 (10), 461 (10)
XIId	$C_{34}H_{41}N_5O_2$	55	551 (*M*, 54), 517 (15), 504 (100), 502 (7), 491 (17), 489 (24), 478 (43)
XIIe	$C_{37}H_{45}N_5O_4$	91	623 (*M*, 100), 578 (28), 577 (30), 562 (11), 548 (64), 492 (45), 491 (17), 478 (16), 475 (30)
XIIf	$C_{38}H_{47}N_5O_2$	80	603 (*M*, 82), 536 (18), 530 (5), 492 (90), 491 (100), 476 (38), 461 (38)

developed in [4] (some of them are presented in Table 1) we established that the reaction of meso-aminomethylprophyrins with hydroxy-containing compounds is an extremely general process. The principal conditions that must be observed in the synthesis of the ethers are thorough purification of the solvent and the use of excess zinc acetate and alcohol.

The assumption of the development of intermediate activated complex XI, which is capable of reacting with nucleophiles, made it possible to extend this reaction to the synthesis of the most diverse meso-substituted porphyrins. We investigated one of the most important, in our opinion, reactions, viz., the reaction with CH acids, since interesting compounds that contain (in the meso position of the porphyrin ring) a functional group that is not conjugated with the macroring can be obtained in this case. It was observed that the reaction rate and, as a final result, the yield of the reaction product are in good agreement with the pK_a values of the corresponding CH acids. For example, in the series [5] CH_3COCH_3 (pK 20) > CH_3NO_2 (pK 10.6) > $CH_3COCH_2COCH_3$ (pK 9) ~ $CH_2(CN)COOC_2H_5$ (pk 9) > $CH_2(NO_2)CH_2COOC_2H_5$ (pK 5.8) the reaction proceeds with the greatest difficulty with acetone, whereas it is complete in a few minutes with nitroacetic ester, and the product is obtained in quantitative yield. The XIIa-f structures were confirmed by data from the electronic, IR, PMR, and mass spectra.

The electronic spectra of XIIa-f depend only slightly on strong electronegative groups in the meso substituent and resemble the spectrum of meso-methyletioporphyrin. The certain bathochromic shift (up to 2-4 nm) in the case of compounds with a branched side chain (XIIc,e,f) is evidently due to steric factors.



XII a-f

XII a $R=CH_2COCH_3$; b $R=CD_2COCD_3$; c $R=CH(COCH_3)_2$; d $R=CH_2NO_2$; e $R=CH(NO_2)COOC_2H_5$; f $R=CH(CN)COOC_2H_5$

The mass spectra of XIIa-f usually contain intense peaks of molecular ions and a peak with m/e 491,

which corresponds to β cleavage. In addition, peaks of ions with m/e values greater than 491, which in each case are individual and correspond to fragmentation of the molecular ions, are present in the spectra.

Of the PMR spectra of XIIa-f, which confirm their structures, one may note the spectrum of porphyrin XIIe, on the basis of which, from the pronounced shielding of the ester ethyl group due to the ring current, it may be assumed that the meso substituent is located under the plane of the porphyrin ring.

Thus, the results obtained with respect to the synthesis of diverse porphyrins in the basis of copper [2] and zinc [2] complexes of meso-dimethylaminomethyletioporphyrin I constitute evidence for the ease of cleavage of the C–N bond with splitting out of dimethylamine and the formation of a stabilized cation in the case of protonation or in the case of the formation of a complex with a Lewis acid (zinc acetate in this case) at the nitrogen atom of the dimethylaminomethyl group.

We assumed that thermal cleavage of the C–N bond is also possible when metal complexes of meso-aminomethylporphyrins are heated in a high-boiling alcohol with the subsequent formation of an ether bond. In fact, complexes (XIII and XIV) of porphyrin IIIg were isolated in 90 and 81% yields, respectively, when copper and nickel complexes of porphyrin VIII were heated briefly in freshly distilled ethylene glycol. A similar experiment with free porphyrin VIII did not lead to the production of the corresponding ether IIIg. Consequently, the presence of a central metal atom (Cu^{2+}, Ni^{2+}, Zn^{2+}, and possibly others) in the porphyrin molecule is absolutely necessary for cleavage of the C–N bond and the formation of a reactive carbonium ion, while the mode of activation of the meso-aminomethyl group (protonation, the formation of a complex with Lewis acids, or thermolysis) is not of fundamental significance.

A report [6] that the formation of alkoxymethylporphyrins (in the case of the synthesis of two meso-ethoxymethyloctaalkylporphyrins) occurs with the prior formation of a metalloporphyrin by means of the usual treatment of the corresponding labile meso-acetoxymethyl derivative with ethanol was recently published. However, this method evidently cannot be used as extensively as the method that we described because of the difficulties involved in the preparation of meso-acetoxymethylporphyrins when labile substituents are present in the porphyrin ring in the latter.

EXPERIMENTAL

The electronic spectra of solutions of the compounds in chloroform were recorded with an MPS-50L spectrometer. The IR spectra were obtained with a model 180 Perkin–Elmer spectrometer. The PMR spectra of solutions of the compounds in $CDCl_3$ were obtained with HA-100D and XL-100 spectrometers with hexamethyldisiloxane as the internal standard. The mass spectra were obtained with an MAT-311 mass spectrometer. The chromatographic separation and purification of the porphyrins were realized with a column filled with L40 × 100 silica gel (Czechoslovakian SSR).

meso-Alkoxymethylporphyrins (IIIa-k, Table 1). A mixture of 100 mg of porphyrin VIII, 200-300 mg of zinc acetate, 3-5 ml of the corresponding alcohol, and 25 ml of carbon tetrachloride or anhydrous tetrahydrofuran (THF) was refluxed until zinc complex X, which remains at the start during chromatography of a sample on Silufol in chloroform, was no longer present in the reaction mixture. From 5-10 min to 102 h was usually required for completion of the reaction. The reaction mixture was then evaporated in vacuo, the residue was treated with hot water, and the undissolved zinc complex of alkoxymethylporphyrin was removed by filtration and dissolved in chloroform. The chloroform solution was shaken with 2-3 ml of dilute hydrochloric acid (1:3) for 5 min, and the organic layer was separated, washed with water and ammonium hydroxide, filtered through a layer of aluminum oxide, and chromatographed with a column filled with silica gel. The principal fraction was evaporated, and the substance was crystallized from a mixture of chloroform and methanol. Since the electronic spectra of chloroform solutions of all of the compounds are very similar, we will present only some of them [compound, λ_{max} (nm), and $\varepsilon \cdot 10^{-3}$ given]: IIIe, 406 (165), 508 (13.2), 543 (8.9), 577 (5.9), 630 (4.2); IIIf, 408 (164), 509 (12.1), 545 (7.6), 580 (5.5), 631 (3.4); IIIh, 406.5 (154), 506 (12.2), 541 (8.5), 577 (5.8), 631 (4.4); IIIj, 406 (175), 507 (13.1), 544 (8.8), 577 (6.0), 630 (4.9).

Reaction of meso-Dimethylaminomethyletioporphyrin (VIII) with CH Acids. The reaction was carried out as in the case of the method described above. Only CCl_4 was used as the solvent. The yields and data from the mass spectra are presented in Table 1.

5-Acetylmethyl-2,7,12,17-tetramethyl-3,8,13,18-tetraethyl-21H,23H-porphine (XIIa). UV spectrum, λ ($\varepsilon \cdot 10^{-3}$): 409 (20.5), 508 (13.8), 543 (5.9), 577 (5.9), 628 hm (1.6). IR spectrum: ν 1720 cm^{-1}. PMR spectrum, δ: 9.97 (s, 2H), 9.73 (s, 1H, meso-H), 5.35 (m, 2H), α-H), 3.46 (3H), 3.51 (6H), 3.54 (3H, all s, CH_3

ring), 3.99 (211), 3.96 (2H), 3.93 (4H, all q, CH_2CH_3), 1.78 (311), 1.77 (3H), 1.73 (6H, all t, CH_2CH_3), 3.01 (2H, dd, CH_2CO), 3.51 (s, 3H), 2.65 (2H, NH); in $CDCl_3$ + 1% CF_3COOH: 10.16, 10.13 and 10.00 (all s, meso-H), 5.19 (m, 2H, α-H), 3.49 (m, 2H, CH_2XO), 3.39 ppm (s, $COCH_3$). The corresponding deutero analog XIIb was obtained by heating porphyrin VIII with d_6-acetone.

5-(2,2-Diacetylmethyl)-2,7,12,17-tetramethyl-3,8,13,18-tetraethyl-21H,23H-porphine (XIIc). UV spectrum, λ_{max} ($\varepsilon \cdot 10^{-3}$): 411 (18.2), 511 (12.9), 547 (6.8), 582 (5.7), 633 hm (1.8). IR spectrum: ν_{CO} 1710 and 1732 cm^{-1}. PMR spectrum, δ: 9.95 (2H), 9.79 (1H, all s, meso H), 5.64, (m, α-H), 3.48 (3H), 3.51 (6H), 3.52 (3H, all s, CH_3 ring), 3.98 (8H, m, CH_2CH_3), 1.69 (12H, m, CH_2CH_3), 3.50 ppm (3H, s, $COCH_3$).

5-(2-Nitroethyl)-2,17,12,17-tetramethyl-3,8,13,18-tetraethyl-21H,23H-porphine (XIId). UV spectrum, λ_{max} ($\varepsilon \cdot 10^{-3}$): 409 (16.2), 508 (13.1), 542 (6.4), 577 (5.7), 628 hm (2.4). IR spectrum: ν_{NO_2} 1550 cm^{-1}. PMR spectrum, δ: 10.05 (2H), 9.92 (1H, all s, meso-H), 5.93 (m, α-H), 3.50, 3.55, 3.58, 3.60 (all s, CH_3 ring), 4.01 (m, CH_2CH_3), 1.78 (m, CH_2CH_3), 4.90 ppm (m, CH_2NO_2).

5-(2-Nitro-2-ethoxycarbonylethyl)-2,7,12,17-tetramethyl-3,8,13,18-tetraethyl-21H,23H-porphine (XIIe). UV spectrum, λ_{max} ($\varepsilon \cdot 10^{-4}$): 411 (16.4), 510 (12.4), 547 (7.1), 582 (5.4), 634 hm (2.8). IR spectrum: ν_{CO} 1760 cm^{-1}; ν_{CO} 1570 cm^{-1}. PMR spectrum, δ: 10.03 (2H), 977 (1H, all s, meso H), 6.14 (d, α-H), 5.48 (t $CHNO_2$), 3.66 (3H), 3.59 (6H), 3.54 (3H, all s, CH_3 ring), 4.2-3.8 (m, CH_2CH_3), 1.96-1.67 (m, CH_2CH_3), 3.34 (q, OCH_2), 0.03 ppm (t, OCH_2CH_3).

5-(2-Cyano-2-ethoxycarbonylethyl)-2,7,12,17-tetramethyl-3,8,13,18-tetraethyl-21H,23H-porphine (XIIf). UV spectrum, λ_{max} ($\varepsilon \cdot 10^{-3}$): 410 (19.6), 510 (13.2), 546 (7.5), 581 (5.7), 632 hm (2.8). IR spectrum: ν_{CO} 1755 cm^{-1}; the $\nu_{C\equiv N}$ band does not appear. PMR spectru, δ: 10.01 (2H), 9.81 (1H, all s, meso H), 5.86 (m, α-H), 3.49 (3H), 3.54 (6H), 3.58 (3H, all s, CH_3 ring), 3.97 (m, CH_2CH_3), 1.78 (m, CH_2CH_3), 3.66 (m, OCH_2), 0.56 (split t, OCH_2CH_3), −3.03 ppm (2H, NH).

Nickel Complex (XIV of 5-(2-Hydroxyethoxymethyl)-2,7,12,17-tetramethyl-3,8,13,18-tetraethyl-21H, 23H-porphine. A 40-mg sample of the nickel complex of meso-dimethylaminomethyletioporphyrin I (obtained by the method in [7] by formylation of the nickel complex of etioporphyrin I) was refluxed in 20 ml of dry distilled ethylene glycol, during which the starting complex dissolved completely and the color of the solution changed from lilac to cherry-red. The solution was cooled and treated with 80 ml of water, and the substance was extracted with chloroform and chromatographed with a column filled with silica gel in a chloroform–ether system (95:5). The first fraction contained a small amount of the nickel complex of etioporphyrin. The second and principal fraction was evaporated to dryness, the residue was dissolved in 5 ml of ether, and 30 ml of petroleum ether (bp 70-100°C) was added to the solution. The maximum was evaporated in vacuo to 15 ml, and the concentrate was allowed to stand in the cold for several days. The finely crystalline precipitate was separated to give 33.5 mg (81%) of complex XIV. The product was very soluble in acetone, ether, and chloroform. UV spectrum, λ_{max} ($\varepsilon \cdot 10^{-3}$) 406 (18.4), 534 (8.5) 572 hm (15.8). PMR Spectrum, δ: 936 (s, 3H, meso H), 5.91 (s, 2H, CH_2O), 3.72 (q, 8H), CH_2CH_3), 3.61 (t, 2H, CH_2CH_2OH), 3.54 (t, 2H, CH_2OH), 1.63 (6H), 1.60 (3H), 1.58 ppm (3H, all t, CH_2CH_3). Mass spectrum for $C_{35}H_{32}N_4O_2$ ^{58}Ni, m/e (relative intensity, %): 608 (M^+, 100), 563 (6), 548 (75).

Copper Complex (XIII) of 5-(2-Hydroxyethoxymethyl)-2,7,12,17-tetramethyl-3,8,13,18-tetraethyl-21H,23H-porphine. This complex was similarly obtained from the copper complex of meso-dimethylaminomethyletioporphyrin by heating in ethylene glycol for 5 min. Slow cooling of the solution produced bright-red prismatic needles of the chromatographically pure complex XIII (in 90% yield). UV spectrum, λ_{max} ($\varepsilon \cdot 10^{-3}$): 412 (181), 534 (8.5), 572 hm (15.8), Mass spectrum for $C_{35}H_{42}N_4O_2$ ^{63}Cu, m/e (relative intensity, %): 613 (M^+, 100), 568 (5), 553 (70).

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BENZINDOLES. 21.* NITRATION OF 3-FORMYL[4, 5]-AND 3-FORMYL[6,7] BENZINDOLES

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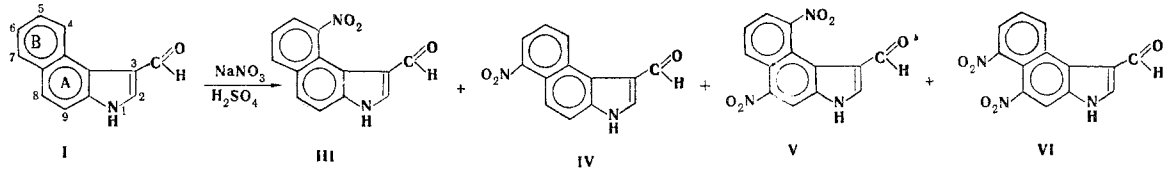
It was established that products of monosubstitution of 4-nitro- and 7-nitro-3-formyl[4,5] benzindoles and products of disubstitution of 4,8-dinitro- and 7,8-dinitro-3-formyl[4,5] benzindoles are formed in low yields in the nitration of 3-formyl[4,5]benzindole with sodium nitrate in concentrated sulfuric acid. Similar nitration of 3-formyl[6,7]benzindole leads to 9-nitro- and 5,6-dinitro-3-formyl[6,7]benzindoles. The 3-formylnitrobenzindoles obtained were converted to nitrovinyl derivatives by condensation with nitromethane.

The regularities in the behavior of indole in electrophilic substitution reactions, particularly in nitration, have been studied extensively and correlated [2, 3], and the nitration of 3-formylindoles has also been studied [4-6]. However, the introduction of an additional benzene ring in the indole molecule has a substantial effect on the course of the reaction [7-9]. Not enough information is available in the literature to enable one to draw an unambiguous conclusion regarding the behavior of condensed indole structures in electrophilic substitution reactions, the orientation of the substituents, and the possibilities for their preparative utilization.

The aim of the present research was to study the behavior of 3-formyl[4,5]- (I) and 3-formyl[6,7]benzindole (II), which were obtained by modified methods [10, 11], in nitration and the possibilities of the preparation of 3-formylbenzindoles with a nitro group in the benzene ring. Considering the fact that the nitration of indole derivatives in weak acids leads to side reactions (addition to the C_2-C_3 multiple bond, replacement of an acyl group by a nitro group, etc.), we carried out the nitration in concentrated sulfuric acid. Sodium nitrate was used as the nitrating agent.

Complex mixtures of compounds are formed as a result of nitration both in the case of 3-formyl[4,5] benzindole (I) and in the case of 3-formyl[6,7]benzindole (II). We were able to isolate four compounds, two of which are monosubstituted compounds, viz., 4-nitro- (III) and 7-nitro-3-formyl[4,5]benzindole (IV), and two disubstituted compounds, viz., 4,8-dinitro- (V) and 7,8-dinitro-3-formyl[4,5]benzindole (VI), from the products of the nitration of benzindole I.



I III IV V VI

We were able to isolate only two stable compounds, viz., 9-nitro- (VII) and 5,6-dinitro-3-formyl[6,7] benzindole (VIII), from the products of the nitration of benzindole II.

*See [1] for Communication [1].

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