NITRATION OF BENZO[g]ISOQUINOLINE AND ITS METHYL-SUBSTITUTED DERIVATIVES

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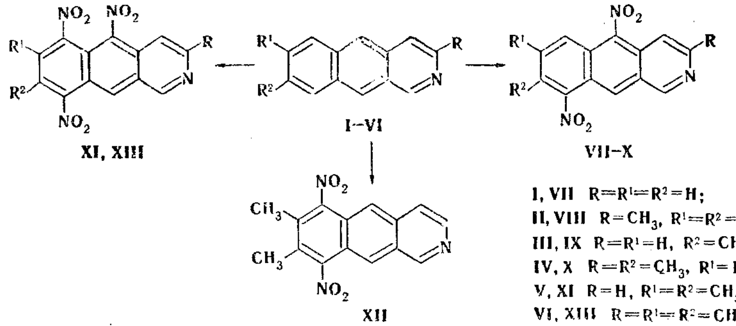
Di- and trinitro derivatives are formed in the nitration under mild conditions (0-5°C) of benzo[g]isoquinoline and its analogs with a methyl substituent in the pyridine and phenylene rings. The principal reaction products contain a nitro group in the meso position (attached to the C_5 atom) and in the phenylene ring. The structures of the nitro derivatives obtained and the position of the nitro groups in the molecules were proved by means of the PMR, IR, and mass spectra.

Despite the fact that benzo[g]isoquinoline is a relatively simple heterocyclic system, very little information regarding its properties is available. The synthesis of a limited number of representatives of azaanthracenes has been described in several studies devoted to these heterocycles [1-6], and the oxidation of one of them to the corresponding azaanthraquinone has been demonstrated. Other transformations in the benzo[g]isoquinoline series, particularly electrophilic substitution reactions, have not been studied, but the literature does contain theoretical assumptions regarding possible reaction centers (from the electron-density distributions) of benzo[g]isoquinoline [7].

Having a relatively practicable method for the preparation of benzo[g]isoquinoline and its methyl-substituted derivatives at our disposal [6], we studied their ability to undergo electrophilic substitution in the case of nitration. As the subjects of the investigation we used benzo[g]isoquinoline and its 3-methyl, 8-methyl, 3,8-dimethyl, 7,8-dimethyl, and 3,7,8-trimethyl derivatives (I-VI), which were obtained in our laboratory. Nitration was carried out at 0-5°C with a 20-fold excess of the nitrating mixture.



XI, XIII

I-VI

VII-X

XII

I, VII $R = R^1 = R^2 = H$;
II, VIII $R = CH_3$, $R^1 = R^2 = H$;
III, IX $R = R^1 = H$, $R^2 = CH_3$;
IV, X $R = R^2 = CH_3$, $R^1 = H$;
V, XI $R = H$, $R^1 = R^2 = CH_3$;
VI, XIII $R = R^1 = R^2 = CH_3$

We were unable to detect mononitro derivatives in any of the experiments on the nitration of benzo[g]isoquinolines I-VI, although the reaction was carried out under mild conditions. Dinitro derivatives VII-X were obtained in rather high yields from benzo[g]isoquinoline I and its mono- and dimethyl derivatives II-IV, whereas trinitro derivatives XI and XIII were obtained from benzo[g]isoquinolines V and VI. Dinitro derivatives XII was also obtained in low yield in the nitration of V.

The analytical data and data from the IR and mass spectra (Tables 1 and 2) of nitro derivatives VII-XIII unambiguously confirm their compositions, viz., the presence of two or three nitro groups. The solution of the problem of the position of the nitro groups in the nitro compounds is, of course, essential. This information would make it possible to determine the principal pathways of electrophilic substitution reactions in the case of benzo[g]isoquinolines. We drew preliminary conclusions regarding the structures of

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TABLE 1. Spectral Data for the Nitro Derivatives (VII-XIII) of Benzo[g]isoquinolines

Compound	mp, °C	UV spectrum, λ_{max} (log ε), nm	IR spectrum,	Mass spectrum, m/z values (relative intensities, %)
VII	255—257	255 (4,82), 291 (3,82), 364 (3,56), 400 (3,76), 420 sh (3,64)	1540, 1360, 1340	M^+, 269 (100); $[M-NO_2]^+$, 223 (40,4); $[M-2NO]^+$, 209 (47,6); $[M-NO_2, -NO]^+$, 193 (52,4); $[M-2NO_2]^+$, 177 (71,4); $[M-NO, -CO]^+$, 211 (40,4); $[M-2NO, -CO]^+$, 181 (47,6)
VIII	266—267	247 (4,76), 258 (4,74), 345 (3,43), 363 (3,55), 406 (3,57)	1520, 1360, 1340	M^+, 283 (100); $[M-NO]^+$, 253 (9,23); $[M-NO_2]^+$, 237 (9,25); $[M-2NO]^+$, 223 (16,6); $[M-NO_2, -NO]^+$, 207 (20,3); $[M-2NO, -CO]^+$, 195 (16,6); $[M-2NO_2]^+$, 191 (22,2); $[M-NO_2, -NO, -CO]^+$, 179 (29,6); $[M-2NO, -2CO]^+$, 167 (18,5); $[M-2NO_2, -HCN]^+$, 164 (31,4)
IX	249—251	255 (4,89), 290 (3,76), 332 (3,50), 352 (3,56), 386 (3,72), 400 (3,76)	1520, 1355	M^+, 283 (100); $[M-NO_2]^+$, 237 (17,3); $[M-2NO]^+$, 223 (18,9); $[M-2NO_2]^+$, 191 (27,5); $[M-2NO, -CO]^+$, 195 (13,7); $[M-NO_2, -NO, -CO]^+$, 179 (41,4); $[M-2NO, -2CO]^+$, 167 (20,7); $[M-2NO_2, -HCN]^+$, 164 (43,1)
X	225—227	256 (5,08), 332 (3,45), 352 (3,38), 410 (3,53)	1510, 1380, 1360	M^+, 297 (100); $[M-NO]^+$, 267 (22,7); $[M-NO_2]^+$, 251 (18,1); $[M-NO, -OH]^+$, 250 (22,7); $[M-2NO]^+$, 237 (36,3); $[M-NO_2, -NO]^+$, 221 (54,5); $[M-2NO, -CO]^+$, 209 (27,2); $[M-2NO_2]^+$, 205 (40,9); $[M-NO_2, -NO, -CO]^+$, 193 (54,5); $[M-2NO, -2CO]^+$, 181 (36,3); $[M-2NO_2, -HCN]^+$, 178 (45,5)
XI	302—304	260 (4,90), 345 (3,64), 400 (3,66)	1535, 1370	M^+, 342 (100); $[M-H_2O]^+$, 324 (8,3); $[M-NO]^+$, 312 (7,1); $[M-NO_2]^+$, 296 (79,7); $[M-NO_2, -NO]^+$, 266 (48,8); $[M-2NO_2]^+$, 250 (39,3); $[M-2NO_2, -NO]^+$, 220 (73,8)
XII	272—274	260 (4,72), 340 (3,23), 368 (3,32), 406 (3,48), 420 sh (3,40)	1545, 1380	M^+, 297 (100); $[M-2NO]^+$, 237 (26,5); $[M-NO_2, -NO]^+$, 221 (34,4); $[M-2NO, -CO]^+$, 209 (20,6); $[M-2NO_2]^+$, 205 (40,6); $[M-NO_2, -NO, -CO]^+$, 193 (46,8); $[M-2NO, -2CO]^+$, 181 (23,4); $[M-2NO_2, -HCN]^+$, 178 (28,1)
XIII	252—254	263 (4,81), 340 (3,40), 364 (3,37), 415 (3,64)	1530, 1370	M^+, 356 (46,1); $[M-H_2O]^+$, 338 (11,5); $[M-NO]^+$, 326 (11,5); $[M-NO_2]^+$, 310 (80,7); $[M-NO_2, -NO]^+$, 280 (100); $[M-2NO_2]^+$, 264 (23,0); $[M-2NO_2, -NO]^+$, 234 (57,6)

TABLE 2. Results of Elementary Analysis of the Nitro Derivatives (VII-XII) of Benzo[g]isoquinolines

Compound	Found, %			Empirical formula	Calculated				Yield, %
	C	H	N		C, %	H, %	N, %	M	
VII	58,0	2,7	16,0	$C_{13}H_7N_3O_4$	58,0	2,6	15,6	269	70
VIII	59,7	3,2	14,7	$C_{14}H_9N_3O_4$	59,4	3,2	14,8	283	35,5
IX	59,3	3,5	14,3	$C_{14}H_9N_3O_4$	59,4	3,2	14,8	283	71,6
X	52,5	3,1	16,1	$C_{15}H_{10}N_4O_6$	52,6	3,2	16,2	342	48,4
XI	60,5	4,0	14,0	$C_{15}H_{11}N_3O_4$	60,6	3,7	14,1	297	5,2
XII	54,1	3,5	15,4	$C_{16}H_{12}N_4O_6$	54,1	3,4	15,7	356	55,6

nitro derivatives VII-XIII on the basis of an analysis of the PMR spectral data, which are presented in Table 3. Considering the fact that the methyl groups in the investigated nitro derivatives are found in different amounts (0-3) in various positions of the cyclic system and in various orientations with respect to the nitro substituents, by means of the double-resonance method we were able to unambiguously assign the signals in the spectra of

TABLE 3. Parameters of the PMR Spectra [δ(ppm) and J (Hz)] of Di- and Trinitro Derivatives (VII-XIII) of Benzo[g]isoquinolines

	1-H	3-H	4-H	5-H	6-H	7-H	8-H	10-H
VII*	9,24 br s	7,72 br s	7,11 d† J=7,0	—	7,4—7,6††	6,68 dd J=9,0, 7,2	7,4—7,6††	9,12 br s
VIII*	9,29 br s	2,1 d J=0,75	7,11**	—	7,4—7,6††	6,69 dd J=9,0, 7,2	7,4—7,6††	8,99 br s
IX*	8,95 br s	7,73 br s	7,25 d J=7,0	—	7,39 d J=9,0	6,72 d J=9,0	1,96 br s	8,45 br s
X*	8,89 br s	2,07 d J=0,75	7,06 q	—	7,37 d J=9,25	6,59 d J=9,25	1,85 br s	8,45 br s
XI‡	8,67 br s	8,24 d J=6,47	7,22 dt J=6,47, 1,0	—	—	1,62 (1,64) br s	1,64 (1,62) br s	7,92 br s
XII‡	8,96 br s	8,33 br s	6,97 d J ~ 5,8	7,82 br s	—	1,68 s	1,68 s	7,97 br s
XIII‡	8,52 br s	2,37 d J ~ 1,0	7,26 sext J ~ 1	—	—	1,52 (1,55) s	1,55 (1,52) s	7,89 br s

*In C_6D_6COOH.

†Only the strong-field conponent of the doublet is visible.

‡In C_6D_6.

**Narrow unresolved m.

††Unresolved m.

the di- and trinitro derivatives obtained and were able to establish that the nitro groups are found in the 5 and 9 positions in the dinitro derivatives and in the 5, 6, and 9 positions in the trinitro derivatives. The dinitro derivative of 7,8-dimethylbenzo[g]isoquinoline, which was isolated in small amounts along with trinitro derivative XI, contains nitro groups in the 6 and 9 positions. Although benzo[g]isoquinoline differs from condensed binuclear and trinuclear homo- and heteroaromatic systems in that only polynitro derivatives are formed during its nitration under mild conditions, the general principles of nitration also remain valid for this aromatic system: A nitro group is not incorporated in the pyridine ring; primary attack evidently takes place in the meso position, which is the farthest away from the heteroatom (C_5); the second nitro group is incorporated in the unsubstituted phenyl ring; the presence of a methyl substituent increases the probability of incorporation of a nitro group in the phenylene ring in which the substituent is found, and primary attack takes place at the C_9 atom. The establishment of the structures of the polynitro derivatives obtained will be reported in greater detail in a separate publication.

EXPERIMENTAL

The PMR spectra of solutions of the compounds in C_6D_6 and C_6D_6/CF_3COOH were obtained with a Bruker WP-80 spectrometer with tetramethylsilane as the internal standard. The IR spectra of KBr pellets of the compounds were recorded with UR-20 and IR-75 spectrometers. The UV spectra of solutions of the compounds in $CHCl_3$ were recorded with a Specord UV-vis spectrophotometer. The mass spectra were measured with an MKh-1303 mass spectrometer at an ionizing voltage of 70 V.

5,9-Dinitrobenzo[g]isoquinoline (VII). A 2-g (0.01 mole) sample of benzo[g]isoquinoline (I) was added in portions at −5 to 0°C in the course of 1 h to a nitrating mixture [7.7 ml (0.17 mole) of nitric acid (sp. gr. 1.37 g/ml) and 17.56 ml (0.34 mole) of sulfuric acid (sp. gr. 1.87 g/ml)], and the mixture was stirred at 0-5°C for 3 h. It was then poured over ice, and the aqueous mixture was neutralized (pH 10) with sodium carbonate. The precipitate (2.35 g) was washed with water, dried, and crystallized from toluene to give 2.1 g of dark-yellow crystals of VII.

The nitration of benzo[g]isoquinolines II-IV and VI was carried out similarly. 5,9-Dinitro derivatives VIII-X, respectively, were obtained from II-IV, while 5,6,9-trinitro derivative XIII was obtained from VI. Compounds VIII-X and XIII were dark-yellow substances.

7,8-Dimethyl-5,6,9-trinitro- and 7,8-Dimethyl-6,9-dinitrobenzo[g]isoquinolines (XI, XII). A 2.0-g (0.01 mole) sample of benzo[g]isoquinoline V was added in portions at −5 to 0°C to a nitrating mixture [8.88 ml (0.2 mole) of nitric acid (sp. gr. 1.37 g/ml) and

20.9 ml (0.4 mole) of sulfuric acid (sp. gr. 1.87 g/ml)], and the mixture was stirred at 0-5°C for 3 h. It was then poured over ice, and the resulting precipitate was removed by filtration, washed with water, dried, and crystallized from toluene to give 1.6 g of trinitrobenzo[g]isoquinoline XI. The aqueous solution was neutralized (pH 10) with sodium carbonate, and the resulting precipitate was washed with water, dried, and crystallized from benzene to give 0.15 g of dinitrobenzo[g]isoquinoline XII.

Data on VII-XIII are presented in Tables 1 and 2.

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SYNTHESIS AND STEREOCHEMISTRY OF BENZO[a]CYCLOHEXANO[f]QUINOLIZIDINES OF THE 8-AZA-D-HOMOESTRANE SERIES

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A mixture of trans,anti, cis- and cis,anti,cis-quinolizidines in a ratio of $\sim$1:4, respectively, was obtained (in $\sim$10% yield) in the thermal condensation of 4-methyl-4-acetylcyclohex-2-en-1-one with 3,4-dihydroisoquinoline.

Recently in a preliminary communication [1] we described the simple synthesis of analogs of 8-aza-D-homoestrane that contain a methyl substituent attached to C_{13} by means of the thermal condensation of cyclohexenone (I) with 3,4-dihydroisoquinoline (II) (to give the product in $\sim$10% yield). We also accomplished this reaction at a pressure of 14000 atm [2], which made it possible to increase the yields of the desired products significantly. In all cases stereoisomers Va, b are formed in a ratio of 1:4, which evidently reflects the difference in the ease with which the plane of the immonium fragment in intermediate IV, which arises from initial betaine III [1], undergoes attack by the acetyl carbanion. The results of a study of the structures and stereochemistries of the indicated isomers are examined in the present communication.

It follows from the data from the IR and ^{1}H NMR spectra that benzo[a]cyclohexano[f]-quinolizidines Va, b have different stereochemistries, which are due primarily to differences in the fusion of the B and C rings. Thus, in conformity with the known criterion [3, 4], trans-B/C fusion should be assigned to minor reaction product Va, since intense Bohlmann bands at 2760 and 2810 cm^{-1} are present in its IR spectrum, while a resonance signal (the X part of the ABX spectrum) of the benzyl 11b-H proton is found at 3.71 ppm (in $CDCl_3$). Bohlmann bands are absent in the IR spectrum of preponderant isomer Vb, and the signal of the benzyl proton has a chemical shift of 4.16 ppm (in $CDCl_3$); this indicates cis-B/C fusion in this isomer. It is apparent from the data in Table 1 that the vicinal

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