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MONONITRATION OF DERIVATIVES OF BENZISATINS

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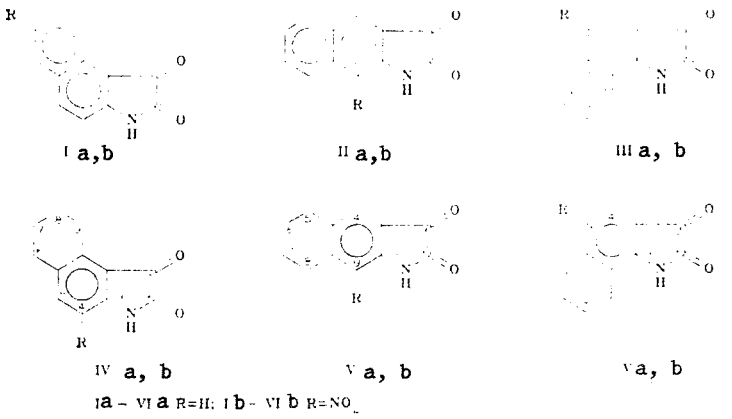
The mononitration of benz[e]-, benz[f]-, and benz[g]isatins and their tetrahydro derivatives was realized. It was established on the basis of an analysis of the ^{1}H NMR and mass spectra that substitution takes place at position 5 in the derivatives of the [g] series and at the position adjacent to the NH group in derivatives of the [f] series and in the case of 6,7,8,9-tetrahydrobenz[e]isatin. This reaction path corresponds to the maximum electron density in the HOMO, calculated by the CNDO method. In benz[e]isatin, contrary to the general relationship and to the quantum-chemical prediction, the nitro group initially enters the ring annellated with the indole ring.

Published data on the introduction of a nitro group into the aromatic part of the benzindole system mostly concern compounds containing alkyl groups in the pyrrole ring [1-4]. Thus, it was shown, on the basis of data from the PMR spectra of nitro derivatives [3] and the corresponding amines [4], that mixtures of compounds are formed during the nitration of angular dimethylbenzindoles, but the nitro group always enters the ring which is annellated to the indole ring.

We studied the direction of the mononitration of benz[e]-, benz[f]-, and benz[g]isatins (Ia-IIIa) and their tetrahydro derivatives (IVa-VIa).



Ia – VIa R=H; Ib – VIb R=NO$_2$

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TABLE 1. Calculated Electron Densities in the HOMO (ρ_i) of Benzisatins, $\times 10^3$

Compound	Atom					
	4	5	6	7	8	9
Ia	394	81	202	334	220	52
IIa	240	308	211	71	384	401
IIIa	151	396	323	89	155	277
IVa	345	74				
Va	74					92
VIa	45	131				

Here, in view of the different effect of the dioxopyrrole fragment on the naphthalene fragment compared with the dimethylpyrrole fragment, corresponding differences could be expected in the direction of nitration, especially as this is indicated indirectly by certain other electrophilic substitution reactions of benzisatins and, in particular, by sulfonation [5]. The formation of mixtures in the nitration reactions of indoles containing alkyl and related groups at positions 2 and 3 is also known [6], whereas the nitration of isatins takes place initially at position 5 and only then at position 7 [7]. The essential differences in the various types of biological activity of 5- and 7-substituted nitroisatins should also be noted [7, 8].

For quantum-chemical prediction of the reaction we calculated the reactivity indices of the initial benzisatins by the CNDO method. The choice of geometric model and method was substantiated in detail in [9, 10]. Since the reaction takes place at one of the reaction centers in the aromatic part of the molecule with the formation of a transitional complex of the π type, the populations in the HOMO (ρ_i), which is a π-type MO in all the investigated compounds, were chosen as reactivity criterion. According to this criterion (Table 1), the electrophilic substitution reaction must take place at the center with maximum electron density in the HOMO. Thus, in the series of benzisatins (Ia-VIa) it is predicted that the nitro groups will enter the benzene ring annellated with the dioxopyrrole ring, and this differs fundamentally from the experimental data on the titration of dimethylbenzindoles [3].

The nitration of isatin derivatives with a mixture of nitric and sulfuric acids leads to high yields of 5-nitroisatins [11]. In our case this method is suitable for tetrahydrobenzisatins, whereas its use for the titration of the aromatic derivatives (Ia-IIIa) leads to mixtures of compounds (TLC). This is due to the presence of a larger number of reaction centers in the annellated naphthalene fragment. More selective mononitration of compounds (Ia-IIIa) is achieved by the selection of specific versions of the method using acetic acid (see Experimental).

In order to obtain evidence for the structure of the obtained mononitro products we used primarily PMR spectroscopy. Since in the series of mononitro derivatives of the hydrogenated compounds with respect to only one aromatic proton even its assignment created obvious difficulties, we undertook an analysis of the PMR spectra of series of previously synthesized derivatives of benzisatins [12, 13], and this secured an unambiguous assignment of the signals in the initial compounds (Table 2). Then, as a rule, we estimated the approximate descreening effect of the nitro group on the remaining protons in the molecule and constructed possible theoretical PMR spectra for the various versions of nitro substitution.

Thus, the presence of two systems of protons with spin–spin coupling constants of 8.67 and 9.11 Hz, respectively, in the spectrum of the mononitrobenz[e]isatin indicates substitution at position 7 or 8, and substitution at $C_{(7)}$ is more likely; in this case, the effects of the nitro group on the chemical shifts in the obtained mononitro derivative (Ib) compared with the initial (Ia) ($\Delta\delta_i$) are as follows: $\Delta\delta_6 = 105$, $\Delta\delta_8 \approx 70$-100, $\Delta\delta_9 = 22$ Hz. Approximately the same $\Delta\delta_i$ values, due to the effect of the nitro group at the ortho and meta positions, respectively, were observed earlier for derivatives of the benzene [14] and benzindole [3] series. (With the alternative possible structure of 8-nitrobenz[e]isatin it would be supposed that $\Delta\delta_6 = 64$, $\Delta\delta_7 \approx 70$-100, $\Delta\delta_9 = 63$ Hz, i.e., that the nitro group has practically the same effect both on the ortho- and on the meta-protons, and this can hardly be possible in reality.)

TABLE 2. PMR Spectra of Benzisatins (Ia-VIa) and Mononitrobenzisatins (Ib-VIb)

Compound	δ, ppm							J, Hz
	4-H	5-H	6-H	7-H	8-H	9-H	NH, s	
Ia	8,12 d	7,10 d	7,84 dd	7,2...7,7 m		8,30 d	10,80	$J_{45}=8,5$; J_{56}, J_{67}, $J_{68}=9$; J_{68}, $J_{79}=1,5$
Ib	8,58 d	7,41 d	9,01 d	—	8,41 dd	8,55 d	11,47	$J_{45}=8,67$; $J_{68}=2,42$; $J_{89}=9,11$
IIa	8,18 d	7,6...8,0 m (s, 8-H)	7,2...7,6 m		7,6...8,0 m (s, 5-H)	7,11 d	10,29	J_{56}, J_{67}, $J_{78}=8$; J_{45}, $J_{89}=0,8$; J_{57}, $J_{68}=1,5$
IIb	8,49 d	8,0...8,3 m (s 8-H)	7,4...7,9 m		8,0...8,3 m (s, 5-H)	—	11,82	$J_{45}=0,8$; J_{56}, $J_{78}=8$; J_{57}, $J_{68}=1,5$
IIIa	7,39 q		7,85 d (or 8,10)	7,4...7,7 m		8,10 dd (or 7,85)	11,57	J_{67}, J_{78}, $J_{89}=9$; J_{68}, $J_{79}=1,5$
IIIb	8,15 s	—	8,24 dd (or 8,45)	7,6...8,0m		8,45 dd (or 8,24)	12,22	J_{67}, J_{78}, $J_{89}=9$; J_{68}, $J_{79}=1,5$
IVa	6,51 d	7,13 d					10,73	
IVb*	—	7,92 s					11,37	$J_{45}=9$
Va*	7,07 s					6,48 s	10,77	
Vb*	7,32 s					—	11,37	
VIa*	7,10 d	6,65 d					10,80	$J_{45}=8$
VIb	7,80 s						11,37	

*The signals for the protons of the cycloalkane fragment are not given in the table.

TABLE 3. Peak Intensities of the Characteristic Ions in the Mass Spectra of Compounds (Ib-VIb) ($\%\Sigma_{50}$)

Compound	W_M	$[M-CO]^{+\cdot}$	$[M-OH]^+$	$[M-NO_2]^+$	$[M-CO-NO]^+$	$[M-CO-NO_2]^+$	$[M-OH-CO]^+$	$[M-OH-NO]^{+\cdot}$
Ib	9,8	15,0	—	—	1,6	2,9	—	—
IIb	13,1	2,1	7,7	2,0	1,0	1,6	1,8	9,0
IIIb	13,2	15,8	—	—	1,3*	—	—	—
IVb	7,6	1,0	12,3	5,5	—	0,8	1,0	13,3
Vb	1,1	0,3	1,8	0,8	—	—	0,4	1,9
VIb	7,6	1,0	12,3	5,5	—	0,8	1,0	13,3

*In addition, there are the ions $[M - CO-NO-CO]^+$ 3.9%, $[M - CO-NO-HNCO]^+$ 2.2%, $[M - CO-NO-HNCO-H]^+$ 11.1%.

Multiplet signals corresponding to the four protons of the ring annellated to the indole ring are seen in the spectrum of mononitrobenz[f]isatin, and the general form of this part of the spectrum corresponds to the initial benz[f]isatin (IIa) with a downfield shift of the signals by approximately 20 Hz. Thus, it can be supposed that substitution occurs only at $C_{(4)}$ or at $C_{(9)}$. Since the chemical shifts of these protons in the initial compound (IIa) are known on the basis of analysis of the spectra of benz[f]isatin derivatives [15] (Table 2), the mononitro product must be assigned the structure of 9-nitrobenz[f]isatin; in this case, the doublet at 8.49 ppm with J = 0.8 Hz corresponds to the proton at $C_{(4)}$, and the descreening effect of the nitro group on this proton at the para position is $\Delta\delta_4 \approx 20$ Hz. (If it is assumed that substitution takes place at $C_{(4)}$, then $\Delta\delta_9 \approx 120$ Hz, which is unlikely for para-substitution.) Consequently, the structure of 9-nitrobenz[f]isatin (IIb) is most probable for the mononitro product which forms.

The formation of 5-nitrobenz[g]isatin (IIIb) is confirmed by the presence of a distinct signal at 8.15 ppm in its PMR spectrum. The effect of the nitro group on the chemical shift of the proton at $C_{(4)}$ is $\Delta\delta_4 \approx 70$ Hz; as in the case of benz[f]isatin (IIa), the spectrum of the proton in the ring annellated with the indole ring undergoes small changes, expressed in the approximately uniform descreening ($\Delta\delta_i$ amounts to between 25 and 45 Hz), as a result of nitration.

It is also possible to obtain evidence for the structure of the mononitro derivatives of tetrahydrobenzisatins (IVb-VIb) on the basis of an analysis of the PMR spectra of series of derivatives of tetrahydrobenzisatins substituted at the NH and β-carbonyl group [12, 13, 16] and subsequent determination of the descreening effect of the nitro group, as was done above for the aromatic derivatives. It should be noted that in the series of tetrahydrobenzisatins, as also in the usual substituted derivatives of the isatin series [7], nitration takes place at the atom corresponding to position 5 of the isatin (indole) ring. If there are substituents at this position, substances analogous with 7-nitroisatin are formed. Here (VIa) is nitrated most readily and with a good yield, while the introduction of a nitro group at the position adjacent to the NH group is complicated; more clearly-defined steric hindrances evidently also appear in the case of the derivative (Va).

In order to confirm the presence or absence of the nitro group at the position adjacent to the NH group we studied compounds (Ib-VIb) by mass spectrometry, taking account of the known differences in the mass-spectrometric behavior of the 5-nitro derivatives [17] and 7-nitro derivatives [18] of indolin-2-ones. In the series of mononitro derivatives of the aromatic benzisatins, as follows from the data in Table 3, only the mass spectrum of compound (IIb) contains a strong peak for the $[M - OH]^+$ ion, and this characterizes the ortho arrangement of the nitro group and the NH fragment of the isatin part of the molecule. On the other hand, such an ion is not formed in the mass spectra of (Ib) and (IIIb), in which the nitro group is separated from the hydrogen-containing substituent, and the process which takes place most vigorously in the dissociation of the molecular ion is the loss of the CO molecule, which is typical of the majority of isatin [7, 17] and benzisatin [12] derivatives.

In the mass spectra of the tetrahydro derivatives (IVb-VIb) the $[M - OH]^+$ ion is formed on account both of the protons of the NH group and of the adjacent CH_2 group of the cycloalkane fragment. This further confirms the conclusions made on the basis of the PMR spectra about the point of entry of the nitro group.

The presence of the nitro group at the position adjacent to the NH naturally increases the chromatographic mobility of the compounds (see the TLC data in Table 4). This must also be explained by the formation of intramolecular associates.

By correlation of the obtained data it can be seen that in most cases the mononitration of benzisatins, in contrast to other benzindoles so far investigated, takes place in the ring annellated with the dioxopyrrole ring. This can be explained by features of the effect of this ring on the distribution of charge in the annellated naphthalene (or hydrogenated naphthalene) fragment and agrees well with the data from quantum-chemical calculation. The exception is benz[e]isatin (Ia), for which the preferential occurrence of the reaction in the ring annellated with the indole ring has been proved unambiguously. This disagrees with the quantum-chemical prediction. In this case there are clearly additional reasons (energy, steric) which require a more extensive study of the electrophilic substitution reactions in the benz[e]indole series.

TABLE 4. Characteristics of the Mononitrobenzisatins (Ib-VIb)

Compound	Molecular formula	mp, °C*	R_f	Yield %	Compound	Molecular formula	mp, °C*	R_f	Yield, %
Ib	$C_{12}H_6N_2O_4$	306...308	0,29	62	IVb	$C_{12}H_{10}N_2O_4$	222...223	0,82	53
IIb	$C_{12}H_6N_2O_4$	275	0,77	49	Vb	$C_{12}H_{10}N_2O_4$	195	0,84	24
IIIb	$C_{12}H_6N_2O_4$	300...302	0,52	91	VIb	$C_{12}H_{10}N_2O_4$	228	0,63	82

*The solvent for crystallization was aqueous ethanol.

EXPERIMENTAL

The PMR spectra were recorded in DMSO-d_6 on Hitachi R-22 (90 MHz) and Bruker WM-360 instruments with HMDS as internal standard. The mass spectra were recorded on a MAT-212 instrument with direct injection into the ion source at 70 eV.

Thin-layer chromatography was conducted on Silufol UV-254 in the 1:1 carbon tetrachloride–ethyl acetate system, and the spots were detected in visible and UV light. The initial benzisatins were obtained by known methods, and their characteristics were given in [12]. The data from elemental analysis for C, H, and N correspond to the calculated compositions.

7-Nitrobenz[e]isatin (Ib). To a suspension of 2 g (10 mmoles) of benz[e]isatin (Ia) in 80 ml of acetic acid we added 15 ml of sulfuric acid, and over 10 min we added dropwise 0.9 ml (11 mmoles) of 58% nitric acid, while keeping the temperature at 45-50°C. The mixture was cooled to room temperature and poured onto ice. The orange precipitate was filtered off, washed with water, and dried, giving 1.5 g (62%) of (Ib) (Table 4).

9-Nitrobenz[f]isatin (IIb). To a suspension of 2 g (10 mmoles) of benz[f]isatin (IIa) in 40 ml of acetic acid we added 5 ml of concentrated sulfuric acid and 0.9 ml (11 mmoles) of 58% nitric acid. The mixture was kept at 45-60°C for 7-8 min. It was then cooled to room temperature and poured onto ice, and the yellow precipitate was washed with water and dried.

5-Nitrobenz[g]isatin (IIIb). To a suspension of 2 g (10 mmoles) of benz[g]isatin (IIIa) in 160 ml of acetic acid we added 0.9 ml (11 mmoles) of 58% nitric acid. The mixture was stirred at 80-90°C for 10 min and cooled. The orange precipitate was filtered off, washed with water, and dried.

4-Nitro-6,7,8,9-tetrahydrobenz[e]isatin (IVb). At 0°C we prepared a suspension of 2 g (10 mmole) of 6,7,8,9-tetrahydrobenz[e]isatin (IVa) in 10 ml of concentrated sulfuric acid. Then, while keeping the temperature at 0-5°C, we added dropwise 1 ml (125 mmoles) of 58% nitric acid. The mixture was stirred at the same temperature for 30 min and was then poured onto ice. The yellow precipitate was filtered off, washed with water, and dried.

9-Nitro-5,6,7,8-tetrahydrobenz[f]isatin (Vb). The compound was obtained from 2 g (10 mmoles) of 5,6,7,8-tetrahydrobenz[f]isatin by analogy with (IVb). The reaction time was increased to 6 h.

5-Nitro-6,7,8,9-tetrahydrobenz[g]isatin (VIb). The compound was obtained from 2 g (10 mmoles) of 6,7,8,9-tetrahydrobenz[g]isatin by analogy with (IVb).

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SYNTHESIS OF ortho- AND para-QUINONES OF THE BENZINDOLE SERIES

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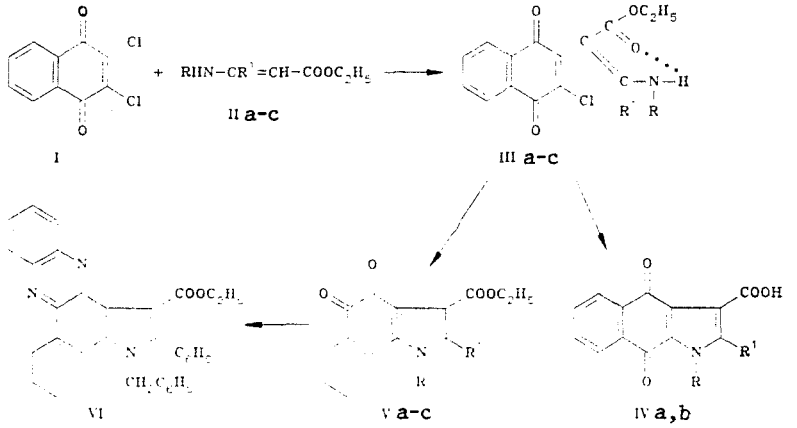
Ethyl esters of α-(3-chloro-1,4-naphthoquinon-3-yl)crotonic or cinnamic acids were obtained by the reaction of 2,3-dichloro-1,4-naphthoquinone with ethyl esters of N-substituted β-aminocrotonic or β-aminocinnamic acids. These esters were converted by alkaline fusion into benz[f]indole-4,9-dione-3-carboxylic acids, and into ethyl esters of benz[g]indole-4,5-dione-3-carboxylic acid by the action of acetic acid.

Linear benzindoles are of interest as compounds with possible biological activity, but are presently difficult to obtain [1, 2]. The aim of the present work was to study a new approach to the synthesis of benz[f]- and benz[g]indoles, containing an o-quinoid type fragment in their structure. In contrast with the previously described [3] method of synthesis of compounds of this type, we chose as the starting compounds 2,3-dichloro-1,4-naphthoquinone (I) and esters of N-substituted β-aminocrotonic (IIa, c) and β-aminocinnamic (IIb) acids. The reaction of quinone I with esters IIa-c leads at the first stage to α-naphthoquinonyl-3-enamino esters IIIa-c, in which the presence of an intramolecular hydrogen bond (IMHB) be-



II—V **a** $R=C_6H_5$, $R^1=CH_3$; **b** $R=CH_2C_6H_5$, $R^1=C_6H_5$; **c** $R=R^1=CH_3$

*Deceased.

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