ACETALS OF LACTAMS AND AMIDES OF ACIDS. 72.* INVESTIGATION OF REACTION OF CYCLIC β-NITROENAMINES WITH p-BENZOQUINONE

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The process of condensation of p-benzoquinone with the secondary cyclic enamines 2-(2-nitromethylene)pyrrolidine, -piperidine, and -hexahydroazepine is very much dependent on the size of the saturated ring in these compounds. With increasing ring size, the content of derivatives of 5-hydroxybenzofuran decreases, and the quantity of derivatives of 5-hydroxyindole increases; with the seven-membered enamine, a substituted 6-hydroxyindole is also formed. For enamines of the pyrrolidine and piperidine series, 1,4-bis-2-(2'-nitromethylene)pyrrolidono- or piperidinohydroquinones are also recovered.

We had established previously that the interaction of tertiary β-nitroenamines with benzoquinone derivatives results in the formation of substituted 3-nitro-5-hydroxybenzofurans [2]. We demonstrated subsequently that secondary β-nitroenamines also enter into the Nenitzescu reaction, forming derivatives of 6-hydroxyindole and 5-hydroxybenzofuran, with the product ratio depending on the size of the substituent on the nitrogen atom of the secondary enamine [1]. The present work has been aimed at investigating the structure of products from the interaction of the secondary cyclic nitroenamines 2-(2-nitromethylene)pyrrolidine (Ia), -piperidine (Ib), and -hexahydroazepine (Ic) with p-benzoquinone (II); the work was further aimed at determining the relationship between the direction of the reactions and the size of the saturated ring in the enamines Ia-c.

Upon condensation of p-benzoquinone with the five-membered enamine Ia, we were able to isolate two primary reaction products. The UV spectrum (in EtOH) of one of these products (IIIa, 34% yield) coincided almost completely with that of the previously described [2] 2-methyl-3-nitro-5-hydroxybenzofuran. In the IR spectrum of this compound, absorption bands were observed corresponding to the OH group at 3360, NH group at 3100-3200 CO of the amide group at 1655, and nitro group at 1370 and 1560 cm^{-1}. These data, together with the PMR data (see Experimental) and the elemental analyses, indicate that 2-γ-acetylaminopropyl-3-nitro-5-hydroxybenzofuran (IIIa) was formed in the course of this reaction. The second compound (20% yield), according to elemental analysis and IR and PMR spectra, corresponds to the structure of 1,4-bis(2-β-nitromethylene)pyrrolidinohydroquinone (IVa).

The yields of the analogous compounds IIIb and IVb when using the six-membered enamine Ib were lower: ~8% of the hydroquinone IVb, 16% of the benzofuran IIIb. Along with these compounds, column chromatography gave small yields of N-acetyl-2-(2-nitromethylene)piperidine (V) and, which is particularly important, 3-nitro-4-acetoxy-5-hydroxy-1,2-tetramethyleneindole (VI). The structure of the latter compound was indicated by mass spectrometry, elemental analysis, consistency of its UV spectrum with that of the corresponding seven-membered analog (see below), and particularly by its PMR spectrum: signals of methylene groups of the saturated ring at 2.05 (m), 3.41 (t), and 4.87 (t), and also 1.85 (s, CH_3CO), 6.80 (d), and 7.10 (d) (aromatic protons), and 10.58 ppm (d, OH), with $J_{6\text{-}H,5\text{-}OH}$ ~0.6 Hz, indicating unambiguously the presence of an acetoxy group in position 4 (not position 5) of the indole ring.

Thus, with an increase in size of the enamine ring, we observe not only benzofuran cyclization, but also the formation of an indole derivative, even though the latter is obtained with a very low yield.

Thus, a further increase of ring size in the secondary enamine, i.e., the change to 2-(2-nitromethylene)tetrahydroazepine (Ic), made it completely impossible to obtain the substituted benzofuran; among the substances that were isolated, we could identify only derivatives of 1,2-pentamethyleneindole. In this case the process was not at all clear-cut, and individual compounds could be recovered only by column chromatography; the product yields were extremely low, and the basic method for proving

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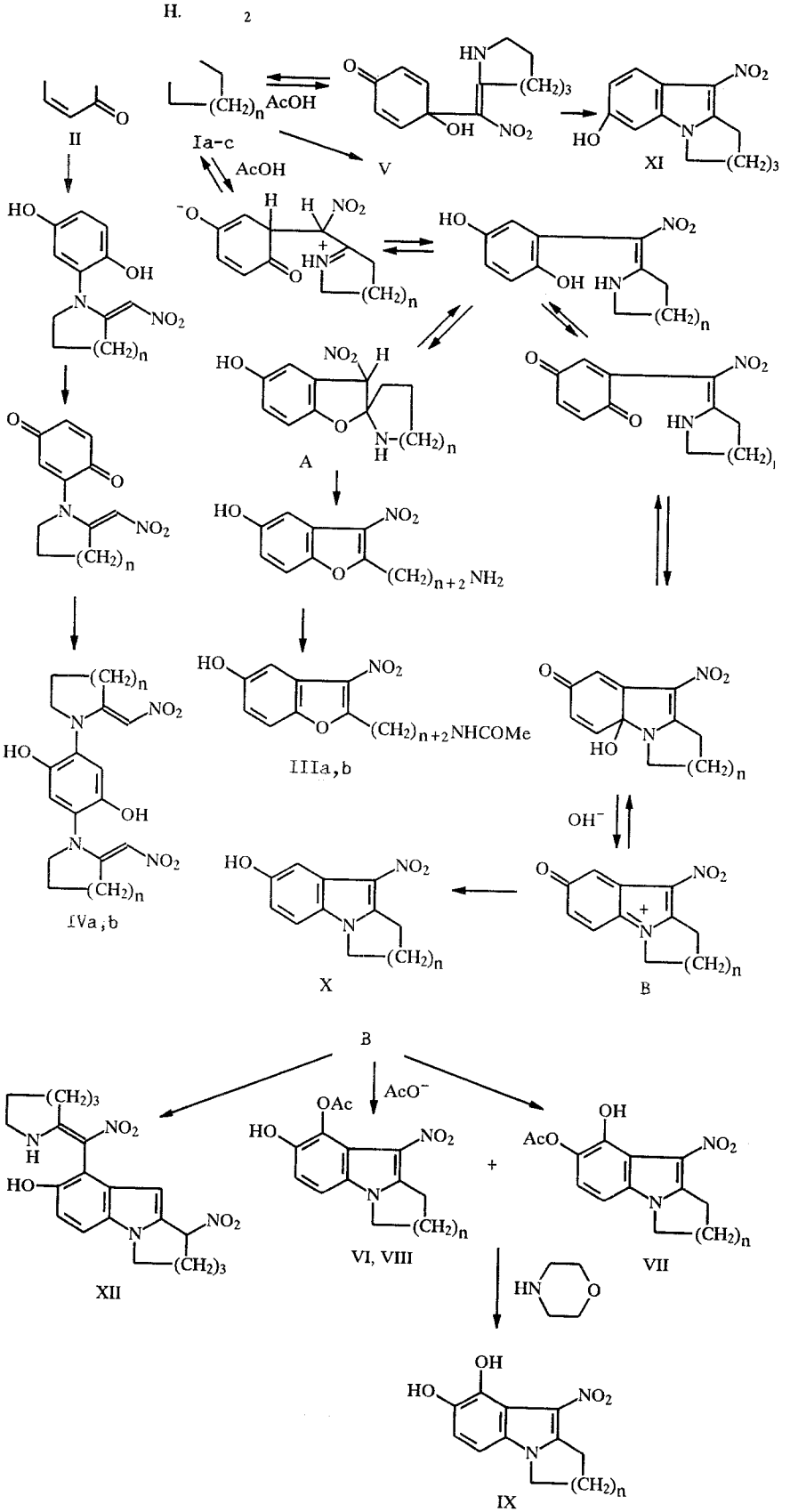
their structure was PMR spectroscopy. Upon elution of the column with chloroform, we first recovered crystals that gave a single spot in TLC. The most characteristic IR band was that at 1760 cm^{-1} ($OCOCH_3$). However, in the PMR spectrum (DMSO-D_6), we observed signals of protons of two related substances: compound VII with bands at 2.28 ($COCH_3$), 6.95 (d) and 7.45 (d) (aromatic protons), and 10.22 (OH); and compound VIII with bands at 2.27 ($COCH_3$), 7.08 (d) and 7.22 (d) (aromatic protons), and 9.33 ppm (OH). Signals of the protons of the seven-membered rings were observed in the 1.70-4.37 ppm region. O-Deacylation of this mixture led to the formation of 3-nitro-4,5-dihydroxy-1,2-pentamethyleneindole (IX), PMR spectrum (DMSO-D_6): 1.69, 1.85, 3.90, 4.34 (CH_2), 6.8 (d) and 7.05 (d) (aromatic protons), and 8.68 and 10.0 ppm (OH). For proof that we had obtained the 4,5-dihydroxy isomer (not the 6,7 isomer), the signal of the methylene protons at 4.34 ppm was saturated, whereupon the increase of the intensity of the 7.05 ppm signal was 27%,* thus providing unambiguous evidence in favor of the structure IX. It should be noted that by recrystallization of the mixture of compounds VII and VIII we were able to isolate the individual isomer VIII, the UV spectrum of which, as has already been mentioned, practically coincided with that of the six-membered analog VI. Upon further elution with chloroform, we also obtained a mixture of compounds giving a single TLC spot; in the mass spectrum there was an intense peak of a molecular ion with $M^{+\cdot}$ 246; in the PMR spectrum taken in a mixture of $CDCl_3$ and DMSO-D_6, signals of two related compounds were observed: 6.79 (d), 7.50 (d), and 7.51 (d) ppm for the one compound, and 6.85 (d), 6.97 (d), and 7.88 (d) ppm for the other. The signals of the protons of the seven-membered rings were located in the 1.70-4.32 ppm interval. It is significant that the signals at 7.51 ppm for one of the isomers and 6.97 ppm for the other are split by the meta-constant; and thus the indicated spectrum corresponds to a mixture of 5-hydroxy- (X) and 6-hydroxy (XI) derivatives of 3-nitro-1,2-pentamethyleneindole. In order to test this hypothesis, we used the HNOE. Upon saturation of the methylene group signals at 4.32 ppm, the intensity of the 7.50 ppm signal increased by 21% and that of the 6.97 ppm signal by 30%. Thus, we have confirmed that compounds X and XI are the 5- and 6-hydroxyindole derivatives, respectively. And, finally, elution of the chromatographic column with alcohol yielded the individual compound XII, which according to elemental analysis and PMR spectrum corresponds to a structure formed by addition of two molecules of the enamine Ic to benzoquinone (II) with subsequent dehydration. Proof of the presence of substituents in positions 4 and 5 was obtained by saturating the methyl group signal at 4.35 ppm, whereupon the intensity of the doublet at 7.53 ppm was increased by 16%.

Our approach to the results must be very cautious in view of the low total yields of compounds actually segregated and identified, as it is difficult to draw any unambiguous conclusions. Nonetheless, some reasonably firm conclusions can be drawn. An overall scheme of synthesis is shown below for all of the compounds that we have obtained; this scheme incorporates the usual concepts [3, 4] regarding the course of the nenitzescu reaction and the accompanying processes (see scheme below).

It appears to us that the basic relationships in these reactions are determined primarily by steric features of the original cyclic systems and the relative rates of various processes that depend on these features. We observed the formation of the 1,4-bis-substituted hydroquinones IVa, b, based on the addition of the enamine nitrogen to the quinone, only for the five- and six-membered rings. It had been shown previously that the rate of attack through an $sp^{2\prime}$-hybridized nitrogen atom (in a series of lactim esters) decreases with increasing ring size in the series 5 > 6 > 7 [5]; this is explained by the greater steric accessibility in the seven-membered ring. It is possible that an analogous effect is manifested in the process under consideration here, so that the pyrrolidine derivative IVa is formed with the highest yield, whereas its hexahydroazepine analog could not be detected at all. A similar picture is observed in the benzofuran synthesis: In the intermediate spiro compounds of the type A, the cyclic CH_2 and/or NH groups are the most distant from the bulky nitro group when n = 1; and the worst situation is observed for the seven-membered compound (n = 3) (Dreiding molecular models). As a consequence, the formation of the benzofurans IIIa, b proceeds with the highest rate and the highest yield (entirely satisfactory for the Nenitzescu reaction) in the case of the five-membered enamine Ia, considerably poorer for the six-membered analog Ib, and not at all for the enamine of the azepine series Ic (the analogous benzofuran was not found at all in the reaction mixture). In contrast, the possibilities of indole cyclization are apparently determined by the stability of the intermediate tricyclic immonium salt (B). In this case, the least acceptable from the standpoint of energetics is the formation of the immonium salt in the strained pyrroloindole series (n = 1). For the reaction of compounds Ia + II, we could not detect any formation of indole compounds. To a lesser degree, the energy unfavorability of the type-B system determines the course of the reaction of the six-membered enamine Ib with benzoquinone; therefore, even though the yield is low, the pyridoindole VI is recovered from the reaction mixture. In contrast, the considerable conformational mobility of the seven-membered ring is responsible for the relatively high stability of the corresponding immonium cation (B, n = 3); and as a consequence, the compounds recovered in the reaction of the enamine Ic with benzoquinone belong to the 5-hydroxyindole series (IX-XII).†

*The experiment with the homonuclear Overhauser effect (HNOE) was performed on samples that had not been degassed.

†On the basis of the available data, we are not able to explain why the derivative of 6-hydroxyindole XI is formed only in the reaction of the seven-membered enamine Ic and the quinone.



Ia, IIIa, IVa, n = 1; Ib, IIb, IVb, n = 2; Ic, VII-XI, n = 3

TABLE 1. Characteristics and Yields of Compounds III-XII

Compound	Empirical formula	mp, °C (from indicated solvent)	Yield, %
IIIa	$C_{13}H_{14}N_2O_5$	175-176 decomp. (alcohol)	34
IIIb	$C_{14}H_{16}N_2O_5$	141-142 (chloroform)	16
IVa	$C_{16}H_{18}N_4O_6 \cdot 1{,}25 \cdot H_2O$	210 decomp. (methanol)	20
IVb	$C_{18}H_{22}N_4O_6 \cdot H_2O$	320 decomp. (alcohol)	8
V	$C_8H_{12}N_2O_3$	70-71 (petroleum ether)	3
VI	$C_{14}H_{14}N_2O_5$	230 decomp. (alcohol)	1
VII+VIII	$C_{15}H_{16}N_2O_5$	213-215 decomp. (alcohol)	3
IX	$C_{13}H_{14}NO_4$	225 decomp. (alcohol)	19
X+XI	$C_{13}H_{14}N_2O_3$	185-188 (dichloroethane)	3
XII	$C_{20}H_{24}N_4O_5$	193-195 decomp. (dioxane)	6

In connection with the results obtained in the present work, we should also note the synthesis of compounds VI and VIII, which contain an acetoxy group in position 4 of the indole ring. In previous studies, similar processes (attack of an acetate anion at position 4 of type B immonium cations) led ultimately to the formation of 5-acetoxy derivatives [6], a result that was attributed to the favorability of forming an intramolecular hydrogen bond between the 4-OH group and the substituent in position 3 of the indole. If this is true, then a hydrogen bond of this type will be energetically less favorable when a nitro group is participating.

EXPERIMENTAL

The PMR spectra were obtained in a Varian XL-200 spectrometer, internal standard TMS. The course of the reaction and the individuality of the substances were monitored chromatographically on Silufol UV-254 plates in a benzene—methanol system (9:1), development in UV light. The characteristics and yields of the compounds are given in Table 1.

The elemental analyses were in agreement with the calculated values. The original compounds Ia-c were obtained by conventional methods [7-9].

2-γ-Acetylaminopropyl-3-nitro-5-hydroxybenzofuran(IIIa);1,4-Bis(2-β-nitromethylenepyrrolidino)hydroquinone (IVa). To a solution of 1.08 g (10 mmoles) of p-benzoquinone in a mixture of 20 ml of acetic acid and 2 ml of acetic anhydride, while stirring at 20°C, 1.92 g (15 mmoles) of the enamine Ia was added. The mixture was allowed to stand for 24 h. The resulting precipitate was filtered off, washed with acetic acid and water, and dried. Obtained 0.75 g of compound IVa. PMR spectrum (DMSO-D_6): 1.85, 2.53, 3.62 (m, CH_2); 6.73 (s, 3-H, 6-H); 8.71 (s, CH), 9.95 ppm (s, 2-OH, 5-OH).

The acetic acid mother solution was diluted with 100 ml of water; and the precipitate was filtered off, washed with water, and dried. Obtained 0.95 g of compound IIIa. PMR spectrum (DMSO-D_6): 1.76 (s, $COCH_3$); 1.9, 3.12, 3.26 (m, CH_2); 6.89 (q, 6-H); 7.52 (d, 7-H); 7.37 (d, 4-H); 7.93 (t, NH); 9.75 ppm (s, OH). UV spectrum (EtOH), λ_{max} (and log ε): 209 (4.52); 240 (4.22); 291.5 (3.84); 321.5 nm (3.8).

2-δ-Acetylaminobutyl-3-nitro-5-hydroxybenzofuran (IIIb); 1,4-Bis(2-β-nitromethylenepiperidino)hydroquinone (IVb); 3-Nitro-4-acetoxy-5-hydroxy-1,2-tetramethyleneindole (VI); 1-Acetyl-2-(2-nitromethylene)piperidine (V). To a solution of 1.08 g (10 mmoles) of p-benzoquinone in a mixture of 20 ml of acetic acid and 2 ml of acetic anhydride, while stirring at 20°C, 2.13 g (15 mmoles) of compound Ib was added. The mixture was allowed to stand for 24 h, diluted with 100 ml of water, and extracted with methylene chloride (4 × 50 ml). The methylene chloride was evaporated down to a volume of 50 ml, and the solution was cooled. The resulting precipitate was filtered off, washed with methylene chloride, and dried. Obtained 0.46 g of compound IIIb. PMR spectrum ($CDCl_3$ + DMSO-D_6): 1.62 (m, CH_2); 1.86 (t, CH_2); 3.29 (m, CH_2); 1.96 (s, $COCH_3$); 6.80 (t, NH); 6.91 (q, 6-H); 7.30 (d, 7-H); 7.58 (d, 4-H); 9.18 ppm (s, OH).

The mother solution was chromatographed in a column with silica gel, with elution first by methylene chloride and then by alcohol. The methylene chloride was driven off, and then the residue was recrystallized from alcohol. Obtained 0.05 g of compound VI. PMR spectrum ($CDCl_3$): 1.85 (s, $COCH_3$, 2.05 (m, CH_2), 3.4 (t, CH_2); 4.07 (t, CH_2), 6.80 (d, 6-H); 7.10 (d, 7-H); 10.58 ppm (s, OH).

From the alcohol mother solution, recovered 0.05 g of compound V. IR spectrum: 1610 cm^{-1} (N-$COCH_3$). M^+ 184.

The alcohol eluate was evaporated down to 5 ml, and the resulting precipitate was filtered off, washed with chilled alcohol, and dried. Obtained 0.3 g of compound IVb. PMR spectrum (in DMSO-D_6): 1.68-3.51 (m, CH_2); 6.73 (s, 3-H, 6-H); 8.78 (s, CH); 11.57 ppm (br-s, OH).

3-Nitro-5-hydroxy-6-acetoxy-1,2-pentamethyleneindole (VII); 3-Nitro-5-acetoxy-6-hydroxy-1,2-pentamethyleneindole (VIII); 3-Nitro-5-hydroxy-1,2-pentamethyleneindole (X); 3-Nitro-6-hydroxy-1,2-pentamethyleneindole (XI); 2-[2-Nitro-2-(1,2-

pentamethylene-3-nitro-5-hydroxyindol-4-yl)-methylene]hexahydroazepine (XII). To a solution of 1.08 g (10 mmoles) of benzoquinone in a mixture of 20 ml of acetic acid and 2 ml of acetic anhydride, while stirring at 20°C, 1.95 g (12.5 mmoles) of compound Ia was added. The mixture was allowed to stand for 24 h, diluted with 100 ml of water, and extracted with chloroform (4 × 50 ml). The chloroform was evaporated down to 50 ml and chromatographed in a column with silica gel. From the chloroform eluate, the following were recovered successively: 0.1 g of a mixture of compounds VII [PMR spectrum (DMSO-D_6): 2.27 (s, $COCH_3$); 7.22 (d, 7-H); 7.08 (d, 6-H); 9.33 (s, OH); 1.70-4.37 ppm (m, CH_2)], and VIII [PMR spectrum (DMSO-D_6): 2.28 (s, $COCH_3$); 6.95 (d, 6-H); 7.45 (d, 7-H); 10.22 (s, OH); 1.70-4.37 ppm (m, CH_2)]. UV spectrum (EtOH), λ_{max} (and log ε): 215.6 (4.54); 259.5 (3.96); 280.4 (4.00); and 412.0 nm (3.77)], and 0.075 g of a mixture of compounds X [PMR spectrum (DMSO-D_6): 6.79 (d, 6-H); 7.50 (d, 7-H); 7.51 (d, 4-H); 1.70-4.32 ppm (m, CH_2)] and XI [PMR spectrum (DMSO-D_6): 6.85 (d, 5-H); 6.97 (d, 7-H); 7.88 ppm (d, 4-H)]. The column was then eluted with alcohol, recovering 0.25 g of compound XII [PMR spectrum (DMSO-D_6): 6.90 (d, 6-H); 7.53 (d, 7-H); 9.26 (s, OH); 11.54 (t, NH); 1.30-4.35 ppm (m, CH_2)].

3-Nitro-5,6-dihydroxy-1,2-pentamethyleneindole (IX). To a solution of 0.3 g (1 mmole) of a mixture of compounds VII and VIII in 30 ml of benzene, 0.87 g (1 mmole) of morpholine was added, and the mixture was refluxed for 20 h. The reaction mixture was evaporated down to 5 ml and cooled; the resulting precipitate was filtered off, washed with benzene, and dried. Obtained 0.05 g of compound IX. PMR spectrum (in DMSO-D_6): 6.86 (d, 6-H); 7.05 (d, 7-H), 10.00 (s), 8.68 (s) (4-OH, 5-OH); 1.69-4.34 ppm (m, CH_2).

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