HYDROGENATED PHENAZINES AND BENZOXAZOLES BASED ON 2-AMINOCYCLOHEXANE-1,3-DIONES

A. K. Aren and D. V. Bite

UDC 547.864.3'787.3:542.942.4.6

4-Oxotetrahydrobenzoxazoles were obtained by the intramolecular cyclization of 2-acetamidocyclohexane-1,3-diones with acetic anhydride, while hydrogenated phenazines, along with 2-aminocyclohexane-1,3-diones as side products, were obtained by acid hydrolysis. The formation of hydrogenated phenazines from 2-aminocyclohexanediones in acidic media was investigated. The structures of the hydrogenated phenazines and benzoxazoles were confirmed by a study of the reactivities and IR spectra.

A search for the optimum conditions for the synthesis of 2-aminocyclohexane-1,3-diones (IIIa-c) from 2-acetamidocyclohexane-1,3-diones (I) established that orange-colored side products are formed along with the expected 2-aminocyclohexanediones under the conditions of acid hydrolysis [1,2]. This compelled us to assume that either the unlikely intramolecular cyclization of the acetamido derivatives (I) to 4-oxotetrahydrobenzoxazoles (IIb, c) or intermolecular condensation of the resulting 2-aminocyclohexane-1,3-diones to form hydrogenated phenazine systems (IVa-c) occur under the reaction conditions. This is not contradicted by the literature data and essentially recalls the formation of oxazoles from α-acetamido ketones or pyrazines from α-amino ketones [3]. To confirm our hypothesis, we investigated the conditions of the intramolecular cyclization of I and the self-condensation of III in 15% hydrochloric acid.

We were able to accomplish the intramolecular cyclization of Ib,c by refluxing them in acetic anhydride; an attempt to cyclize Ia was unsuccessful. The tetrahydrobenzoxazoles (IIb,c) are colorless, crystalline substances that are quite soluble in water and organic solvents and comparatively resistant to the action of dilute alkali; they undergo cleavage in acids, and colored transformation products appear. In this respect, they differ somewhat from other oxazoles, since the oxazole ring is hydrolytically cleaved only on refluxing in concentrated acids [3].

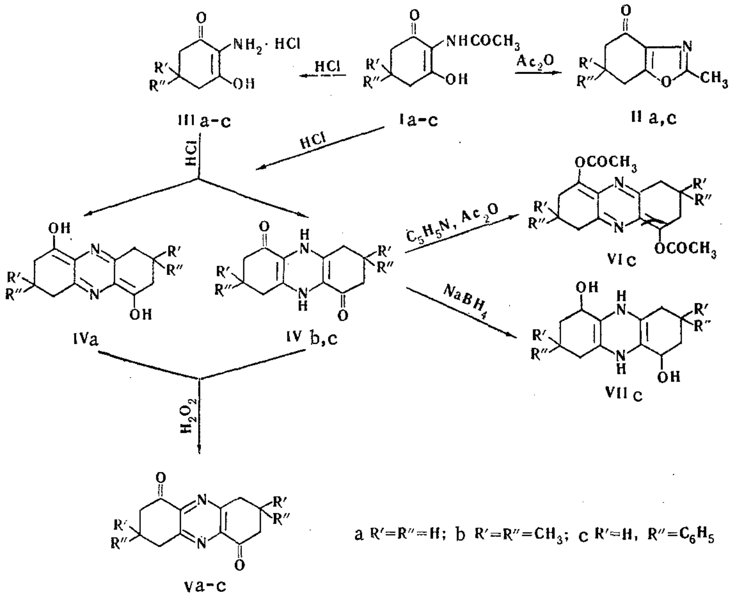
The IR spectra of II contain absorption bands of a carbonyl group at 1687 (IIb) and 1692 cm^{-1} (IIc). The reduction in the frequencies of the vibrations of the carbonyl groups indicates conjugation of the carbonyl group with the oxazole ring [4]. The two frequencies at 1620 and 1592 cm^{-1} (IIb) and 1617 and 1597 cm^{-1} (IIc) can be ascribed to the vibrations of the oxazole ring, while those in the case of IIb can be related to $\nu_{C=C}$ of the benzene ring. In dilute alkali solutions, IIb forms an oxime with hydroxylamine, the IR spectrum of which contains an absorption band of low intensity at 1653 cm^{-1}.

Thus an analysis of the properties and conditions for the formation of IIb,c confirms the previously expressed arguments that tetrahydrobenzoxazole derivatives cannot be formed as side products under the conditions of the hydrolysis of I, since their formation requires other conditions.

Compounds that are identical to the side products obtained in the hydrolysis of I are formed when III are refluxed in 15% hydrochloric acid. Orange substances containing chlorine are formed in all cases. The structure of the hydrochloride of 1,5-dihydroxy-2,3,4,6,7,8-hexahydrophenazine (IVa · HCl) was established for the halogen-containing compound in the case of the condensation of 2-aminocyclohexanedione (IIIa), while in the condensation of IIIb and IIIc the salts are stable only in strongly acidic media; they are hydrolyzed in water, and only the corresponding bases, 1,5-dioxo-3,7-R',R"-1,2,3,4,5,6,7,8,9,10-decahydrophenazines (IVb,c) were investigated in these cases. The yields of the phenazine derivatives and the rates

---

Riga Polytechnical Institute. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 9, pp. 1283-1287, September, 1971. Original article submitted April 20, 1970.



a R'=R''=H; b R'=R''=CH$_3$; c R'=H, R''=C$_6$H$_5$

of cyclization of III are extremely different: in the case of IIIb the hydrogenated phenazine is formed in very low yields even on prolonged refluxing of the solution; in the case of IIIc the yield of the corresponding IVc reaches 78% when the reaction is carried out for 5-6 h, while in the case of IIIa the maximum yield of phenazine (63%) is achieved in 2 h.

It can be assumed that a certain amount of free base is present in aqueous solutions of the salts as a consequence of the reduced basicity of 2-aminocyclohexanediones. Although the existence of aminocyclohexane-1,3-diones in the keto-enol forms with an intramolecular hydrogen bond similar to a betaine has been proved [1], acidic media to some extent promote the formation of a diketone structure, which enters into condensation. The capacity of the bases for participation in condensation and the reaction rates under these conditions depend on the strength of the intramolecular interaction of the OH and NH$_2$ groups. Substituents in the 5 position with their +I or −I effects can affect both the basicity of the NH$_2$ group and the acidity of the OH group and thereby affect the capacity of the aminodiketones for self-condensation.

The hydrogenated phenazines (IVb,c) are only slightly soluble compounds and dissolved only in acetic acid to give bright-violet solutions from which brown products crystallize out of solution. However, on repeated crystallization the solubility improves considerably, the color of the solution changes from violet to yellow, and a yellow modification crystallizes out from the solution. The melting points of the yellow modifications are lower than those of the brown modifications. The two modifications have certain differences in their IR spectra. The brown modification of IVb has $\nu_{C=O}$ at 1703 cm^{-1}, δ_{NH} at 1539 cm^{-1}, and ν_{NH} at 3165 cm^{-1}; $\nu_{C=O}$ for the yellow modification increases slightly to 1710 cm^{-1}, and two bands at 3526 and 3476 cm^{-1} are observed in the region of the frequencies of the vibrations of free N−H bonds. The same regularity is observed for both modifications of IVc: the brown modification has $\nu_{C=O}$ at 1703, $\nu_{C=C}$ at 1604, δ_{NH} at 1555, and ν_{NH} at 3185 cm^{-1}, while $\nu_{C=C}$ frequencies of low intensity also appear at 1635 and 1605 cm^{-1} for the yellow modification, with $\nu_{C=O}$ at 1707 cm^{-1}. The presence of two modifications of the hydrogenated phenazine is apparently associated with the formation of intermolecular associates of the $>N-H\ldots O=C<$ type, which are distinguished by different degrees of association. Because of the extremely limited solubility of the brown modifications of IVb,c and the transition in dilute solutions to the yellow modification, this interesting phenomenon was not studied in solutions by means of UV and IR spectra.

The hydrochloride of IVa is very soluble in water and acetic acid, slightly soluble in alcohols, and insoluble in dioxane; a dark-red salt crystallizes out from aqueous solutions. The IR spectrum of this salt does not contain absorption in the region of the C=O group; absorption bands of low intensity at 1554 and 1540 cm^{-1} must be assigned to the vibrations of a pyrazine ring [4]. There are two intense maxima at 3368 and 3151 cm^{-1} in the region of the frequencies of the N−H and O−H bonds, which, on the basis of the absence of absorption in the region of the C=O groups, should be ascribed to the ν_{OH} frequencies. This salt consequently has the structure of the hydrochloride of 1,5-dihydroxy-2,3,4,6,7,8-hexahydrophenazines. Treatment of an aqueous solution of the salt with potassium bicarbonate solution precipitates the base, to which the structure of 1,5-dihydroxy-2,3,4,6,7,8-hexahydrophenazine (IVa) should be assigned on the basis of the IR spectra. In acetic acid, IVa also has a bright-violet color and crystallizes as the brown substance; the yellow modification is not isolated because of the ready oxidation of IVa. The IR spectrum of IVa does not contain the absorption of C =O groups, and only one ν_{OH} band of medium intensity at 3165 cm^{-1} is observed in the region of the absorption of NH and OH groups.

Like dihydropyrazines [3], decahydro- and hexahydrophenazines (IVa-c) are oxidized in acetic acid solutions in the presence of hydrogen peroxide to 1,5-dioxo-3,7-R',R"-1,2,3,4,5,6,7,8-octahydrophenazines (Va-c). In the process, the bright-violet color of the solution changes to yellow. In the case of IVa, the oxidation proceeds very smoothly, even with air oxygen, and the preparation of pure IVa is fraught with difficulties. The IR spectra of Va-c do not contain ν_{NH} frequencies; carbonyl bands are observed at 1709 (Va), 1703 (Vb), and 1698 (Vc) cm^{-1}.

The reactivities of the hydrogenated phenazines were investigated in the case of the more accessible IVc. Acylation of IVc with acetic anhydride in the presence of pyridine gives bright-yellow 1,5-diacetoxy-3,7-diphenyl-2,3,4,6,7,8-hexahydrophenazine (VIc). Only one intense band of an ester carbonyl group at 1765 cm^{-1} appears in the spectrum of VIc, and ν_{NH} frequencies are absent. Consequently, O-acetylation occurs during the acetylation reaction, since the markedly elevated $\nu_{C=O}$ value is characteristic for enol acetates [5]. This sort of reactivity of dioxodecahydrophenazines is in agreement with the reactivity of benzoylenedihydropyridines. The appearance of absorption maxima at 1643, 1585, and 1533 cm^{-1} also is evidence in favor of this structure. It is known that the aromatic ring of pyrazine has three or four absorption bands of medium intensity at 1340-1670 cm^{-1} [4]. The reduction of IVc with sodium borohydride in alcohol gives 1,5-dihydroxy-3,7-diphenyl-1,2,3,4,5,6,7,8,9,10-decahydrophenazine (VIIc), a colorless, crystalline substance that is quite soluble in polar solvents.

EXPERIMENTAL

4-Oxo-2,6,6-trimethyl-4,5,6,7-tetrahydrobenzoxazole (IIb). A 2.00 g sample of Ib was dissolved by heating in 12 ml of acetic anhydride, and the solution was refluxed for 3 h. The acetic anhydride was removed by vacuum distillation, and the oily residue solidified on standing to give 1.58 g (87%) of IIb with mp 69-70° (from water). Found %: C 66.9; H 7.1; N 7.8. $C_{10}H_{13}NO_2$. Calculated %: C 67.0; H 7.3; N 7.8.

2-Methyl-4-oxo-6-phenyl-4,5,6,7-tetrahydrobenzoxazole (IIc). This compound was similarly obtained in 80% yield from Ic and had mp 106° (from alcohol–ether). Found %: C 79.8; H 5.8; N 6.2. $C_{14}H_{13}NO_2$. Calculated %: C 74.0; H 5.7; N 6.2.

4-Oximino-2,6,6-trimethyl-4,5,6,7-tetrahydrobenzoxazole. A 0.50 g (2.5 mmole) sample of IIb was dissolved in hot 5% alkali, 0.40 g (5.7 mmole) of hydroxylamine hydrochloride was added in portions, and the mixture was refluxed for 1 h. The solution was cooled and neutralized with HCl to give 0.47 g (86%) of an oxime with mp 199-201° (dec., from alcohol). Found %: N 14.6. $C_{10}H_{14}N_2O_2$. Calculated %: N 14.4.

1,5-Dihydroxy-2,3,4,6,7,8-hexahydrophenazine (IVa). A 0.60 g sample of IIIa was dissolved in 2 ml of 15% HCl, and the solution was heated for 2 h on a water bath. The orange precipitate was removed by filtration to give 0.30 g (63%) of the hydrochloride of IVa as dark-red crystals with mp 215-218° (from water). Found %: C 56.8; H 6.0; N 11.2; Cl 13.8. $C_{12}H_{14}N_2O_2 \cdot HCl$. Calculated %: C 56.6; H 6.0; N 11.0; Cl 13.9. A 0.25 g (1.0 mmole) sample of the hydrochloride of IVa was dissolved in several milliliters of water, 0.10 g (1.0 mmole) of potassium bicarbonate was added, and the precipitate of IVa was removed by filtration and immediately crystallized from acetic acid to give 0.10 g (47%) of brown crystals of IVa with mp 200-202°. (The compound is decolorized on melting.) Found %: C 66.3; H 6.2; N 12.6. $C_{12}H_{14}N_2O_2$. Calculated %: C 66.0; H 6.4; N 12.8.

1,5-Dioxo-3,3,7,7-tetramethyl-1,2,3,4,5,6,7,8,9,10-decahydrophenazine (IVb). A) The precipitate obtained by the acid hydrolysis of 24.0 g of Ib [1] was washed with hot water. Recrystallization from acetic acid gave 0.32 g (40% based on Ib) of brown crystals of IVb with mp 260-270° (dec.). On repeated crystallization from acetic acid, the solubility of IVb improved, and the color of the solution changed from violet to yellow. The acetic acid was removed by vacuum distillation, and the residue was crystallized from alcohol to give yellow-green crystals of IVb with mp 210-212°. Found %: C 70.4; H 7.8; N 10.2. $C_{16}H_{22}N_2O_2$. Calculated %: C 70.0; H 8.0; N 10.2.

B) A 0.50 g sample of IIIb was dissolved in 2.0 ml of 15% HCl, and the solution was refluxed for 6-7 h. The precipitate was removed by filtration, and IIIb crystallized in the filtrate. The precipitate on the filter was washed with hot water and crystallized from acetic acid to give 0.05 g (14%) of brown crystals of IVb with mp 260-270° (dec.) that did not depress the melting point of IVb obtained by method A. Found %: C 69.8; H 8.0; N 10.1. $C_{16}H_{22}N_2O_2$. Calculated %: C 70.0; H 8.0; N 10.2.

1,5-Dioxo-3,7-diphenyl-1,2,3,4,5,6,7,8,9,10-decahydrophenazine (IVc). A) The precipitate obtained by the acid hydrolysis of 8.0 g of Ic [1] was washed with hot water and dried to give 0.80 g (13% based on Ic) of IVc as brown crystals with mp 280-290° (dec., from acetic acid). Repeated crystallization from acetic acid or dioxane gave yellow crystals of IVc with mp 250-258°. Found %: C 77.9; H 6.4; N 7.4. $C_{24}H_{22}N_2O_2$. Calculated %: C 77.8; H 6.0; N 7.6.

B) A 2.00 g sample of IIIc was dissolved in 7 ml of 15% HCl, and the solution was refluxed for 6-7 h. The orange precipitate was removed by filtration and washed with hot water to give 1.20 g (78%) of brown crystals of IVc with mp 280-290° (dec., from acetic acid) that did not depress the melting point of IVc obtained by method A. Found %: C 78.4; H 5.7; N 7.8. $C_{24}H_{22}N_2O_2$. Calculated %: C 77.8; H 6.0; N 7.6.

1,5-Dioxo-1,2,3,4,5,6,7,8-octahydrophenazine (Va). A 0.20 g (0.92 mmole) sample of IVa was dissolved in acetic acid, and 0.2 ml of 15% hydrogen peroxide was added dropwise. The color of the solution changed from violet to yellow. The acetic acid was removed by vacuum distillation, and the residue was crystallized from alcohol to give 0.1 g (50%) of yellow Va with mp 235-237°. Found %: C 66.8; H 5.9; N 12.6. $C_{12}H_{12}N_2O_2$. Calculated %: C 66.6; H 5.6; N 12.9.

1,5-Dioxo-3,3,7,7-tetramethyl-1,2,3,4,5,6,7,8-octahydrophenazine (Vb). This compound was obtained like Va in 60% yield from IVb and had mp 202-208° (from alcohol). Found %: C 70.8; H 7.6; N 10.4. $C_{16}H_{12}N_2O_2$. Calculated %: C 70.5; H 7.4; N 10.3.

1,5-Dioxo-3,7-diphenyl-1,2,3,4,5,6,7,8-octahydrophenazine (Vc). This was obtained like Va in 60% yield from IVc and had mp 248-253° (from dioxane). Found %: C 78.4; H 5.5; N 7.8. $C_{24}H_{20}N_2O_2$. Calculated %: C 78.2; H 5.4; N 7.6.

1,5-Diacetoxy-3,7-diphenyl-2,3,4,6,7,8-hexahydrophenazine (VIc). A 0.30 g sample of crude IVc was dissolved by heating in a mixture of 4 ml of acetic anhydride and 4 ml of pyridine, and the solution was allowed to stand at room temperature for 3 h and then heated on a water bath for 1 h. Cooling of the solution precipitated 0.20 g (54%) of VIc as yellow crystals with mp 258-265° (from dioxane). Found %: C 73.9; H 5.6; N 5.8. $C_{28}H_{26}N_2H_4$. Calculated %: C 73.9; H 5.7; N 6.1.

1,5-Dihydroxy-3,7-diphenyl-1,2,3,4,5,6,7,8,9,10-decahydrophenazine (VIIc). Sodium borohydride [0.30 g (8 mmole)] was added to a suspension of 0.74 g (2 mmole) of IVc in 50 ml of ethanol. The following day, the alcohol was removed by distillation, and the residue was washed with water to give 0.67 g (89%) of colorless plates of VIIc with mp 235-237° (from dioxane). Found %: C 77.0; H 6.7; N 7.4. $C_{24}H_{26}N_2O_2$. Calculated %: C 76.9; H 7.0; N 7.5.

The IR spectra were recorded with an IKS-14 double-beam spectrophotometer with NaCl prisms (mineral oil suspensions) or with LiF prisms (hexachlorobutadiene suspensions).

LITERATURE CITED

1. A. K. Aren and Dz. V. Bite, Izv. Akad. Nauk Latv. SSR, Ser. Khim., 246 (1971).
2. A. Treibs and R. Zinnmeister, Ber., 90, 85 (1957).
3. R. Elderfield, Heterocyclic Compounds, Wiley (1961).
4. A. R. Katritzky (editor), Physical Methods in Heterocyclic Chemistry, Academic Press (1971).
5. L. Bellamy, Infra-Red Spectra of Complex Molecules, Methuen (1958).