NITROGEN-CONTAINING BISHETEROCYCLIC SYSTEMS

IV. SYNTHESIS AND STRUCTURE OF 5-HYDROXY-(AMINO)-1-BENZAZOLYLPYRAZOLES*

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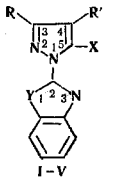
A method has been developed for the synthesis of the previously undescribed hydroxy- and amino-1-benzazolyl-2'-pyrazoles. Examination of the IR spectra and determination of the dipole moments has shown that these derivatives exist in the crystalline form and in solution as the hydroxy and amino forms, which are stabilized by intramolecular hydrogen bonding.

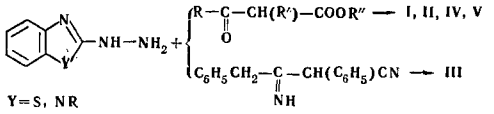
Continuing our investigations into nonplanar bisheterocyclic nitrogen-containing systems [1], we have synthesized the previously undescribed 5-hydroxy- and 5-amino-1-(2'-benzazolyl)pyrazoles (I-V), and investigated their physicochemical properties and structure.



I-V

I $R=C_6H_5$, $R'=H$, $X=OH$, $Y=S$;
II $R=C_6H_5$, $R'=CH_2C_6H_5$, $X=OH$, $Y=S$;
III $R=CH_2C_6H_5$, $R'=C_6H_5$, $X=NH_2$, $Y=S$;
IV $R=CH_2C_6H_5$, $R'=C_6H_5$, $X=OH$, $Y=NH$;
V $R=CH_2C_6H_5$, $R'=C_6H_5$, $X=OH$, $Y=NCH_2C_6H_5$

The 5-hydroxypyrazoles I, II, IV, and V were synthesized from benzazolylhydrazines [2] and β-ketoesters [3] (1), and the 5-amino derivative III, from 2-hydrazinobenzothiazole and benzylphenyliminonitrile (2).



Y=S, NR

Compounds I-V were identified by their analyses, mp's, R_f values (thin layer chromatography on alumina, and on paper [fast, Volodarsk manufacture]), electrophoretic mobilities, UV and IR spectra, and the values of the dipole moments).

In examining the structures of the 5-hydroxy- and 5-aminobenzazolylpyrazoles, we were interested in the following questions:

* For part III, see [12]

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1) The tautomeric forms in which I-V exist in the solid state and in solution.

2) The possible formation of intra- and intermolecular hydrogen bonds.

3) The preferred conformations of molecules I-V.

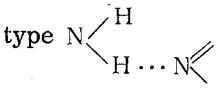
In the IR spectra of I, II, IV, and V in the solid state, no absorption bands are found above 1640 cm^{-1}, possibly indicating that only the hydroxy forms are present in the crystalline state [4]. No significant changes are observed in the benzazolylpyrazoles when the IR spectra are recorded in chloroform. Only in tetrahydrofuran does a weak absorption band appear at 1720 cm^{-1}, perhaps indicating a slight shift of the tautomeric equilibrium toward the keto form [4].

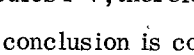
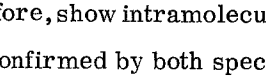
Among the four bands in the 1500-1600-cm^{-1} region attributed to the stretching vibrations of the C=C and C=N bonds, all the compounds I-V show a particularly intense band at 1570-1580 cm^{-1} which, by analogy with [4,5], may be due to the sum of the stretching vibrations of the pyrazole and benzazole rings.

In the LiF-frequency region, I, II, and V show frequencies due to the bound OH group, a wide band with a maximum at 3440 cm^{-1} in the crystalline state, and a narrow band at 3270 cm^{-1} in chloroform. The IR spectrum of the benzimidazole IV in this region deserves special consideration. Unlike the benzthiazoles I and II and the 1-benzylbenzimidazoles V, in the solid state a wide, intense band is found at 2500-3100 cm^{-1}, and a narrow one at 3270 cm^{-1}. The first of these absorptions is characteristic of the stretching vibration of the imino group in the imidazole ring, involved in strong intermolecular hydrogen bonding of the type $\overset{+}{N}H_2 \ldots \overline{N}$ [6], and the second, as mentioned above, may be due to the bound OH group. In chloroform solution, in addition to the vibrations of the bound OH group, low-intensity bands appear at 3430 and 3610-3640 cm^{-1}. We may conclude that, in solution at low concentrations, IV can exist partially in the hydroxy form, with free NH and OH group

Thus, the 5-hydroxy derivatives of 1-benzthiazolyl(2'-imidazolyl)pyrazoles, both in the solid state and in solution, exist predominantly in the hydroxy form. Stabilization of the latter in these compounds is apparently determined by the formation of intra- or intermolecular hydrogen bonds.

The changes observed in the LiF-prism region on passing from the crystalline state to solution indicate clearly [7] the presence of intramolecular hydrogen bonds in I, II, and V. Instead of the wide, diffuse bands at 3300-3500 cm^{-1}, a narrow band appears at 3270 cm^{-1}.

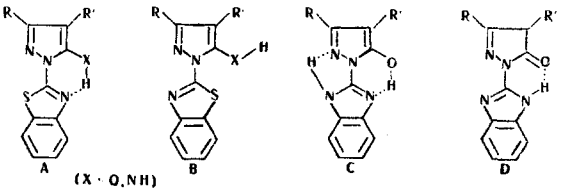
A regularity similar to that described above is seen in the IR spectra of the 5-amino derivatives III. The narrow, clear peaks which appear at 3300 (crystalline state), 3330 (CCl_4), 3400, and 3480 cm^{-1} correspond to the stretching vibrations of the NH_2 group involved in intramolecular interactions of the type  [7]. Actually, the symmetrical stretching vibrations of the NH_2 group (ν_s^{calc}), according to calculation, should occur at 3394 cm^{-1} [8], the deviation from this figure does not usually amount to more than 5 cm^{-1}. In this case, it reaches 64 cm^{-1} ($\nu_s^{calc} - \nu_s^{exp} = 3394 - 3330$ cm^{-1}), which is characteristic for intramolecular hydrogen bonds between one of the H-atoms of the NH_2 group (participation of both the H-atoms in bonding does not destroy the symmetry, and the frequency ν_s^{NH} agrees with that calculated, 3394 ± 5 cm^{-1}).

Molecules I-V, therefore, show intramolecular hydrogen bonding of the  or  type. This conclusion is confirmed by both spectral and dipole moment determinations.

The straight-line relationship between the dielectric permeability and concentration (10^{-3} to 10^{-4} M) shows the absence of association in the solutions of these compounds [9], and, consequently, the absence of intermolecular hydrogen bonds.

5-Hydroxy- and 5-amino-1-(2'-benzthiazolyl)pyrazoles (I-III) can exist in solution in the form of two planar conformers, either with intramolecular hydrogen bonds (A), or without (B) (the sulfur atom of the benzthiazole ring does not usually participate in coordination and the formation of hydrogen bonds), and also with the angular structure involving bending of the azole ring at the N_1-C_2, bond connecting the pyrazole and benzazole fragments of the molecule [1,9]. The similar 1-benzimidazolylpyrazole derivative

IV, in addition to these configurations, can possess the structures C (with two intramolecular hydrogen bonds), or the pyrazolone structure D with intramolecular hydrogen bonds of the $-C=O\ldots H-N$ type.



In order to decide between these conformers, the experimental (μ_{exp}) and calculated (μ_{calc}) values of the dipole moments were compared.

The essentials of the calculation method employed have been described previously [9]. The direction of the dipole moment of the benzthiazolyl fragment was calculated from the experimental values for the moments of thiophene (0.54 D), pyridine (2.2 D), and benzthiazole (1.45 D) [10]. The similar problem in the benzimidazole fragment was solved using the μ_{exp} for 2,4,5-triphenylimidazole (3.92 D), and 2-(p-tolyl)-4,5-diphenylimidazole (3.87 D). The calculation was carried out both for the conformers A-D, and for the other possible models C' (with the OH and NH groups situated on one side of the N_1-C_2 bond in IV), C" (similar to C, but with the direction of the OH vector such that the formation of intramolecular hydrogen bonds is not possible), C"' (similar to C', but with the OH vector directed as in C", and D' (with the C=O group situated on one side of the N_3, nitrogen atom of the benzimidazole ring and the $NH\ldots N_2$ hydrogen bond of the pyrazole ring). Comparison of μ_{exp} and μ_{calc} shows that the experimental values are close to μ_{calc} for configuration A, with intramolecular hydrogen bonds. Thus, for III, $\mu_{exp}=1.59$ D, $\mu_{calc}{}^{A}=1.86$ D and $\mu_{calc}{}^{B}=4.04$ D. In the benzimidazole IV, there is little difference between μ_{exp} (3.37 D) and $\mu_{calc}{}^{C}$ (3.38 D); for $\mu_{calc}{}^{C'}=5.30$ D, $\mu_{calc}{}^{C''}=2.09$ D, $\mu_{calc}{}^{C'''}=6.098$ D, $\mu_{calc}{}^{D}=1.23$ D, and $\mu_{calc}{}^{D'}=6.64$ D.

The difference between the values of μ_{exp} (4.37 D) and $\mu_{calc}{}^{C}$ (3.38 D) is somewhat greater in 5-hydroxy-1'-benzylbenzimidazolylpyrazole (V), possibly as a result of the presence of only one intramolecular hydrogen bond of the $OH\ldots N_3$, type, resulting in a reduction in the stability of the planar structure of type C.

EXPERIMENTAL

5-Hydroxy-(2-benzazolyl)pyrazoles (I, II, IV, and V) were obtained by boiling a mixture of 0.05 mole of the appropriate hydrazine [2] and 0.5 mole of the β-ketoester [3] in 50 ml of tert-butanol, 5 ml of water, and 5 ml of glacial acetic acid for 12 hr. After the solvents were removed in vacuo, the residual hydroxypyrazole was recrystallized from a suitable solvent, and dried in the vacuum desiccator over P_2O_5.

The yields and properties of the compounds are given below. I, yield 73%, colorless plates, mp 201° C (from 80% methanol). Found, %: C 65.08; H 3.32. Calculated for $C_{16}H_{11}N_3OS$, %: C 65.53; H 3.78. UV spectrum (in ethanol): λ_{max} 307 nm, log ε 4.40. R_f Al_2O_3 (i-C_3H_7OH : 2-N NH_4OH : $CHCl_3$ = 20 : 10 : 1) 0.80. R_f on paper (isopentanol-formic acid H_2O = 20 : 4 : 2), 0.85. Electrophoretic mobility (electrolyte 30% acetic acid, pH = 1.4), 14.0. II, yield 76%, colorless needles, mp 165° C (from 80% isopropanol). Found, %: C 71.79; H 4.56. Calculated for $C_{23}H_{17}N_3OS$, %: C 72.05; H 4.47. UV spectrum (in ethanol): λ_{max} 307 nm, log ε 4.48. R_f Al_2O_3, 0.80; R_f on paper 0.91. Electrophoretic mobility 11.7. IV, yield 63%, colorless crystalline plates, mp 224° C (from 80% isopropanol). Found, %: C 75.73; H 5.37. Calculated for $C_{23}H_{18}N_4O$, %: C 75.39; H 4.95. UV spectrum (in ethanol): λ_{max} 290 nm, log ε 4.54. R_f Al_2O_3, 0.67; R_f on paper, 0.70. Electrophoretic mobility 11.7. V, described in [11].

5-Amino-4-phenyl-3-benzyl-1-(2'-benzthiazolyl)pyrazole (III) was prepared by boiling equimolecular amounts of 2-hydrazinobenzthiazole [2], the iminonitrile [11], and 30% HCl in isopropanol. After removal of the solvent and excess HCl with a water pump, the residue was treated with 40% KOH, and extracted with benzene. The benzene was removed, and the compound was recrystallized from 80% methanol to give 60% of colorless needles, mp 163° C (from methanol). Found, %: C 72.35; H 4.99. Calculated for $C_{23}H_{18}N_4S$, %: C 72.24; H 4.74. R_f Al_2O_3, 0.88, R_f on paper, 0.60. Electrophoretic mobility, 13.2.

The IR spectra were obtained on a "Hitachi" spectrometer. The dipole moments of III and V were determined in benzene, and IV in dioxane, at 25° C, by the method described previously [12].

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