SUBSTITUTED 1,10b-DIHYDRO-5H-PYRAZOLO[1,5-c]-1,3-BENZOXAZINES

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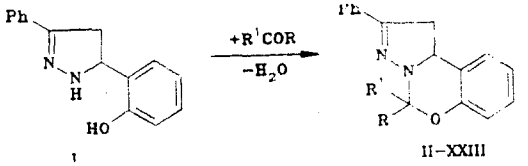
A study was made of the reaction of 3-phenyl-5-(2-hydroxyphenyl)-1H-2-pyrazoline with various aldehydes and ketones, which results in the formation of derivatives of 1,10b-dihydro-5H-pyrazolo[1,5-c]-1,3-benzoxazine.

Benzoxazines annelated with nitrogen-containing heterocycles are of interest due to their potential physiological activity [1, 2]; however, methods available for synthesizing them are very limited [1]. It was therefore of interest to examine the extent to which the cyclocondensation of 3-(4-anisyl)-5-(2-hydroxy-3-methoxyphenyl)-1H-2-pyrazoline with acetone, described in [3], could be used as a general method for the preparation of benzoxazine derivatives.

We have reacted 3-phenyl-5-(2-hydroxyphenyl)-1H-2-pyrazoline (I) with various aldehydes and ketones, leading to the formation of compounds II-XXIII:



I II–XXIII

II–XVI R=H, XVII–XX R=CH_3; II R^1=H, III, XVII R^1=CH_3, IV, XVIII R^1=C_2H_5, V, XIX R^1=C_6H_5, VI R^1=4-ClC_6H_4, VII R^1=4-BrC_6H_4, VIII, XX R^1=4-$O_2NC_6H_4$, IX R^1=4-$(CH_3)_2NC_6H_4$, X R^1=4-$CH_3OC_6H_4$, XI R^1=C_6H_5CH=CH, XII R^1=C_6H_5CO, XIII R^1=4-$C_6H_5C_6H_4CO$, XIV R^1=4-ClC_6H_4CO, XV R^1=4-BrC_6H_4CO, XVI R^1=4-$O_2NC_6H_4CO$, XXI R,R^1=Cyclopentylene, XXII R,R^1=cyclohexylene, XXIII R,R^1=*l*-menthylene

The reaction of pyrazoline I with aromatic aldehydes containing electron-acceptor groups proceeds in boiling methanol and is completed in a few minutes giving quantitative yields of products (compounds V-VII, see Table 1). Contrary to this, 4-substituted benzaldehydes with electron-donor groups undergo cyclocondensation slowly, and the content of resinous impurities in the reaction system is greater. Aliphatic aldehydes and ketones occupy an intermediate position with respect to their reactivity. Arylglyoxals behave similarly.

The cyclocondensation of pyrazoline I with acetophenone could only be realized by boiling it for 2 h 30 min in isopropanol containing catalytic amounts of KOH. It should be noted that benzophenone, benzalacetone, and chalcone do not undergo the reaction with compound I under these conditions. Cyclopentanone and cyclohexanone react similarly to acetone, while l-menthone reacts with pyrazoline only on boiling for 5 h in isopropanol in the presence of KOH.

Compounds V and XXII are also synthesized by boiling the starting compounds in DMFA. In this case the reaction proceeds rapidly, but because of the formation of large amounts of resinous compounds, the yield of the desired end products is lower.

The elemental analysis data and the spectral characteristics correspond to the structure of compounds II-XXII (see Table 1). The main chromophore in these molecules responsible for the longwave absorption band, (C_6H_5—C=N—N), is the same, which accounts for the constancy of the λ_{max} value of this band. In the spectra of products II-XXIII the NH bands (3335 cm^{-1}) and OH bands (3500-3000 cm^{-1}) characteristic for the starting pyrazoline I disappear, and bands of ν_{COC}^{as} 1250 and ν_{COC}^{s} 1160 cm^{-1} of the benzoxazine ring appear.

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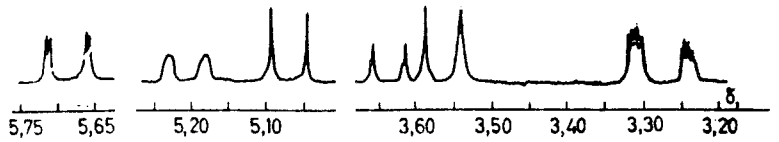

Fig. 1. PMR spectrum of compound II in $CDCl_3$.

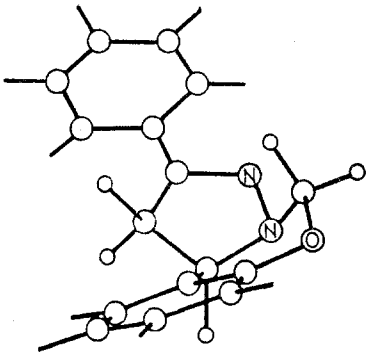

Fig. 2. Dreiding model of the molecule of compound II.

The PMR spectra of compounds I-XXIII are of special interest and, above all, the spectra of protons of the heterocyclic rings (see Table 1). The pyrazoline ring protons in the spectra of all the compounds are characterized by an AMX multiplicity. In the spectrum of the starting compound I they form two quartets (the AM part) and a triplet (the X part) with the CS and SSCC typical for the aromatic derivatives of 2-pyrazolines [4]. The formation of a dihydrooxazine ring substantially influences, above all, the CS of proton A and its vicinal constant J_{AX}. Analysis of the PMR spectrum of compound II (see Fig. 1) shows that proton A undergoes a further spin—spin interaction (J = 0.8-1.0 Hz) with one of the methylene group protons of the oxazine ring which, being diastereotopic, display an appreciable magnetic nonequivalency. Substitution of the methylene protons of the oxazine ring by methyl groups (compound XVII) simplifies the spectrum of the H_A proton (it becomes a doublet of doublets); thus the protons of the methyl groups retain their nonequivalency and their signals differ by 0.42 ppm in their values. Thus, in the spectrum of compound II there was observed a rare case of interaction through five σ-bonds.

To explain this phenomenon, we analyzed the Dreiding model* of the molecule of II (see Fig. 2). It was found that the dihydrooxazine ring has the form of a convert, in which the $C_{(5)}$ atom deviates substantially from the middle plane of the benzoxazine fragment of the molecule. Thus, the pyrazoline ring and the $C_{(5)}$ atom may turn out at one side of this plane (the syn-form) or at different sides (the anti-form). In the syn-form, the axial proton of the oxazine ring and the H_A proton converge to a distance of 2.8-3.0 Å, in between them the p-orbital of the bridgehead nitrogen atom is intercalated. All this probably accounts for the fairly high values of the ^5J constant. On the other hand, the fact of the manifestation of the spin—spin interaction of the H_A and $H_{(5)}$ protons indicates the preference of the syn-form in compound II, caused in turn by the manifestation in it of a stabilizing anomeric effect of the interaction of the p-orbitals of the oxygen atom with the p,π-system of the pyrazoline ring.

The PMR spectra of compounds II and XVII, measured in $CDCl_3$, do not change with time. Another pattern is observed for compounds in which $R \neq R^1$. In these molecules, with the appearance of the second chiral center in the synthesis, the formation of diastereomeric pairs is possible. However, the analysis of the PMR spectra of freshly prepared solutions of most of the compounds in $CDCl_3$ unequivocally indicates the presence of only one diastereomeric pair. When the solutions of these compounds are stored, their spectra become more complex with time at various rates, such that the doubling of the number of the proton signals of the heterocyclic rings is distinctly observed. The signal of the H_A proton for one of the isomers has the form of a well-resolved doublet of doublets, and for the other that of a broadened doublet (in some cases with indications of splitting into several signals). The signals of the diastereomers substantially differ in the values of the chemical shifts, especially for the oxazine ring protons (H_X and $H_{(2)}$, Table 1). The doubling of the number of signals occurs particularly rapidly in compounds XII-XVI — the derivatives of arylglyoxals. In the case of compound XVIII (R = CH_3, R^1 = C_2H_5), it is never possible to obtain a spectrum of one isomer, since a spectrum of a mixture is at once recorded with a 45:55 ratio of isomers,

*The models were prepared in the laboratory of x-ray diffraction analysis of the Adam Mickiewicz Posnan University (Poland) under the direction of Prof. Kaluski.

TABLE 1. Characteristics of Compounds I-XXIII

Compound	Empirical formula	Mp, °C	λ_{max}, nm ($\varepsilon \cdot 10^{-3}$) in i-PrOH	Diastereomer*1	PMR spectrum*2 δ, ppm (SSCC), J, Hz)*4 in $CDCl_3$ R	R'	H_A	H_M	H_X	SSCC, Hz AM	AX	MX	Time of reaction, min	Yield, %*3
I	$C_{15}H_{14}N_2O$	191	—		—	—	2,74	3,43	5,03	−16,2	10,2	10,4	—	—
II	$C_{16}H_{14}N_2O$	126	283 (18,2)		5,06 (d, J = 10,8)	5,68 (d.d, J = 10,8; J = 0,9)	3,29	3,60	5,20	−16,2	1,6	10,0	60	73
III	$C_{17}H_{16}N_2O$	126	284 (17,7)	a	5,16 (q, J = 6,0)	1,94 (d, J = 6,0)	3,24	3,52	5,20	−15,8	1,6	9,8	30	98
III				b	5,94 (q, J = 6,4)	1,60 (d, J = 6,4)	3,32	3,53	5,08	−15,8	1,6	9,8		
IV	$C_{18}H_{18}N_2O$	122	284 (15,6)		4,87 (t, J = 6,6)	2,36 (m, J = 6,6, J = 7,6); 1,18 (t, J = 7,6)	3,21	3,52	5,18	−16,0	1,6	9,8	30	92
V	$C_{22}H_{18}N_2O$	152	285 (21,1)	a	6,89 s	6,7 ... 7,8 m	3,23	3,53	4,76	−16,1	1,5	9,7	30	70
V				b	6,00 s	6,7 ... 7,8 m	3,21	3,51	5,33	−16,1	1,5	9,7		
VI	$C_{22}H_{17}ClN_2O$	143	284 (18,2)	a	6,02 s	6,7 ... 7,8 m	3,27	3,57	5,37	−15,8	1,6	9,4	5	98
VI				b	6,43 s	6,7 ... 7,8 m	3,29	3,59	4,80	−15,8	1,6	9,4		
VII	$C_{22}H_{17}BrN_2O$	194	285 (17,7)		6,66 s	6,7 ... 7,8 m	3,31	3,53	5,52	−16,0	1,4	9,4	5	98
VIII	$C_{22}H_{17}N_3O_3$	182	285 (17,2)		6,27 s	6,7 ... 7,8 m	3,35	3,53	5,46	−16,8	1,4	8,9	3	98
IX	$C_{24}H_{23}N_3O$	203	285 (21,9); 339 sh.	a	6,87 s	2,92 s; 6,7 ... 7,8 m	3,28	3,57	4,86	−15,8	1,6	9,6	120	77
IX				b	5,99 s	3,00 s; 6,7 ... 7,8 m	3,26	3,55	5,37	−15,8	1,6	9,6		
X	$C_{25}H_{20}N_2O_2$	169	286 (22,3)	a	6,40 s	3,77 s; 6,7 ... 7,8 m	3,28	3,57	4,83	−15,8	1,4	9,6	60	95
X				b	6,03 s	3,86 s; 6,7 ... 7,8 m	3,26	3,55	5,37	−15,8	1,4	9,6		
XI	$C_{24}H_{20}N_2O$	140	284 (28,2)		—	—	—	—	—	—	—	—	60	82
XII	$C_{23}H_{18}N_2O_2$	160	250 (19,9); 283 (20,4)	a	6,14 s	6,7 ... 7,8 m	3,29	3,59	5,46	−16,0	1,8	9,4	30	75
XII				b	7,01 s	6,7 ... 7,8 m	3,36	3,60	5,06	−15,8	1,8	9,2		

XIII	$C_{29}H_{23}N_2O_2$	153	284 (32,4)	a	6,54 s	6,7 ... 7,8 m	3,43	3,62	5,05	−16,4	1,8	9,0	45	75
XIII				b	7,02 s	6,7 ... 7,8 m	3,44	3,61	5,60	−16,4	1,8	9,0		
XIV	$C_{28}H_{17}ClN_2O_2$	191	260 (23,2); 279 пл.	a	6,67 s	6,7 ... 7,8 m	3,29	3,52	5,53	−16,2	1,6	9,3	40	66
XIV				b	6,85 s	6,7 ... 7,8 m	3,32	3,53	4,87	−16,2	1,6	9,3		
XV	$C_{23}H_{17}BrN_2O_2$	199	264 (27,5); 281 пл.	a	5,76 s	6,7 ... 7,8m	3,31	3,56	4,89	−16,6	1,6	8,2	40	87
XV				b	6,67 s	6,7 ... 7,8m	3,32	3,55	5,54	−16,6	1,6	9,6		
XVI	$C_{23}H_{17}N_3O_4$	175	273 (26,4)		6,81 s	6,7 ... 7,8m	3,44	3,56	4,89	−16,8	1,8	9,2	30	54
XVII	$C_{18}H_{18}N_2O$	117	284 (16,7)		2,01 s	1,61 s	3,29	3,50	5,14	−15,8	1,6	9,0	20	92
XVIII	$C_{19}H_{20}N_2O$	93	286 (15,5)	a	2,17 s	2,28 (q, J=7,4); 1,05 (t, J=7,4)	3,30	3,50	5,10	−16,0	1,6	9,3	30	95
XVIII				b	1,95 s	2,20 (q, J=7,4); 1,16 (t, J=7,4)	3,28	3,48	5,10	−15,8	1,6	9,2		
XIX	$C_{23}H_{20}N_2O$	131	286 (19,5)		2,16 s	6,7 ... 7,8 m	3,25	3,51	4,81	−16,0	1,4	9,4	150	40
XX	$C_{23}H_{19}N_3O_3$	188	284 (29,4)	a	2,51 s	6,7 ... 7,8 m	3,35	3,57	4,78	−16,6	1,4	9,0	120	44
XX				b	2,69 s	6,7 ... 7,8 m	3,39	3,92	5,32	−18,8	1,4	10,2		
XXI	$C_{20}H_{20}N_2O$	133	286 (19,3)		1,7 ... 2,1 (m, 5H)	2,4 ... 2,6 (m, 3H); 3,29 ... 3,39 (m, 1H)	3,32	3,49	5,14	−16,1	1,8	8,8	60	84
XXII	$C_{21}H_{22}N_2O$	104	286 (17,9)		—	—	—	—	—	—	—	—	90	89
XXIII	$C_{25}H_{30}N_2O$	136	286 (17,5)		—	—	—	—	—	—	—	—	300	76

*[1]a) Spectrum of the diastereoisomer predominating in the reaction mixture; b) spectrum of diastereomer appearing as a result of the acid catalysis.
*[2]Compounds I, III, IV, IX, X, XVII, XVIII, and XXI-XXIII were crystallized from methanol; II, XI, XIX, and XX from isopropanol, V-VIII from dioxane, XII from ethyl acetate, XIII-XVI from toluene.
*[3]The synthesis of compounds III-X, XVII-XIX, and XXI was carried out in methanol, XI-XVI and XX in isopropanol, II, XXII, and XXIII in an isopropanol—KOH mixture ($5 \cdot 10^{-3}$ mole/liter).
*[4]The SSCC of protons of the R and R^1 groups are given.

which shows no further changes. Contrary to this, in the spectrum of compound XIX ($R = CH_3$, $R^1 = C_6H_5$) no doubling of the number of signals takes place with time.

All these data can be convincingly interpreted if it is assumed that trace amounts of DCl (HCl) are present in the solutions, which promote the anomerization of the compounds studied. Since the oxazine ring is a semiaminal, such an anomerizaton is entirely possible. Thus, it should be taken into account that the synthesis of compounds II-XXIII is generally realized in neutral medium and proceeds at a fairly high rate. Under these conditions (the kinetic control of the reaction) one isomer is formed preferentially, while in a $CDCl_3$ solution containing CDCl (HCl) with passage of time, i.e., under the thermodynamic control conditions, an equilibrium between the isomers is established. For compounds II and XVII ($R = R^1$), the anomers are degenerated and, therefore, the spectral pattern is unstable with time.

This conclusion is supported by the fact that the PMR spectra of compounds II and XVII do not change even after prolonged (3-4 h) boiling in $CHCl_3$, while an analogous experiment with compounds III and IX leads to doubling of the number of signals of the protons under consideration. This is additionally confirmed by the data of the PMR spectra measured in neutral solvents: compounds VIII and XXI in deuteromethanol and VII, XII-XVI, and XX in DMSO-D_6. The spectra of all these compounds do not change with time. At the same time, addition of trace amounts of HCl to these solutions cause a doubling of the signals of the pyrazoline and oxazine protons, similarly as described above; the doubling is also accompanied by shifting of the signals into the weak field, probably because of the protonation of the molecules.

In interpreting the PMR spectra of compounds with $R \neq R^1$ we can use the concepts on the preferential existence of the syn-conformer (when in one of the diastereomers the bulky substituent R^1 will be found in an axial position), and to an equal extent consider the equilibrium between the syn- and anti-forms (it can be assumed that in this case the conformational energy of group R compensates the anomeric effect). Unfortunately, it is difficult to obtain an unequivocal answer from the PMR spectra.

The substituted 1,10b-dihydro-5H-pyrazolo[1,5-c]-1,3-benzoxazines II-XXIII are stable in neutral and alkaline solutions, as confirmed by the measurement of their electronic spectra with time. As already mentioned above, protonation takes place in acid medium. Therefore, in the spectra, together with the decrease in the intensity of the band with λ_{max} 283-285 nm, the appearance and increase of the band with λ_{max} 250 nm is observed. The process is reversible, and its equilibrium character is indicated by the presence of an isobestic form. The most probable center of protonation is likely to be the bridgehead nitrogen atom, since the binding of its electron pair will be accompanied by a shortening of the chromophore system, and as a result increase in the color. The protonation at other hetero atoms has no noticeable influence on the absorption spectra.

It should also be noted that the dihydrooxazine ring of compounds II-XXIII is completely hydrolyzed on boiling or holding their acidified (HCl) alcoholic solutions for some time; the initial pyrazoline I is quantitatively recovered from the reaction mixture.

EXPERIMENTAL

The IR spectra of compounds **IV-XXIII** were measured in KBr tablets on a Specord IR-75 spectrophotometer, and the electronic absorption spectra — in isopropanol on a Specord M-40 spectrophotometer at a concentration of the compounds of $(2\text{-}4)\cdot10^{-3}$ mole/liter; the PMR spectra were run on a Gemini-200 Varian spectrometer (200 MHz), using TMS as internal standard. The purity of the compounds was monitored by the TLC method on Silufol UV-254 type plates; chloroform and ethyl acetate were used as eluents.

The initial pyrazoline I was obtained according to the method described in [3].

1,10b-Dihydro-5-methyl-5H-pyrazolo[1,5-c]-1,3-benzoxazine (III). A mixture of 0.48 g (2 mmoles) of pyrazoline I and 0.09 g (2 mmoles) of acetaldehyde was boiled for 25-30 min in a minimal volume of methanol. The precipitate that separated out on cooling was recrystallized from methanol. Yield 0.52 g (98%) of compound III, mp 126°C.

Compounds II and IV-XIII were obtained in a similar manner.

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