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INVESTIGATION OF THE STRUCTURE OF 5-R-3-ARYL-2,1-BENZISOXAZOLES (ANTHRANILS) USING ^{1}H NMR SPECTROSCOPY

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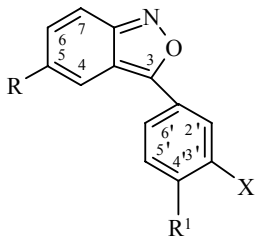
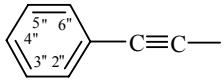
It has been shown that a feature of the ^{1}H NMR spectra of 5-R-3-aryl-2,1-benzisoxazoles is the large difference in chemical shift values for the H(4), H(6), and H(7) protons of the 2,1-benzisoxazole system in each of the compounds but with retention of the overall pattern for the series discussed. It was found that the effect of the heterocycle on the aryl residue in position 3 is equivalent to the effect of a moderately electron accepting group.

Keywords: anthranils, 2,1-benzisoxazoles, ^{1}H NMR spectrum, chemical shift.

The steady growth in interest in heterocyclic compounds is basically connected with their raised biological activity and also with the fact that they make possible the development of novel materials of unique properties. One very interesting and promising class of heterocycles is the series of 2,1-benzisoxazoles or anthranils [1]. We have previously reported features of the synthesis of a series of 5-R-3-aryl-2,1-benzisoxazole heterocyclic compounds [2-4]. It is known that they can serve as starting materials in the preparation of heterocyclic products of other types and they are also intermediate compounds in the synthesis of monomers [5, 6]. However, clearly little concerning the structure and properties of 2,1-benzisoxazoles has been reported. In the current work we present a detailed investigation of the ^{1}H NMR spectroscopic parameters of a series of 5-R-3-aryl-2,1-benzisoxazoles. The chemical shift and proton spin-spin coupling values (*J*) for these anthranils are given in Table 1.



1-6 R^1 = Cl, R^2 = X = H; **1** R = Cl, **2** R = Br, **3** R = I, **4** R = CHO, **5** R = 1,3-dioxolan-2-yl, **6** R = 2-methyl-1,3-dioxolan-2-yl; **7** R^1 = Me, R^2 = X = H, R = Cl; **8-10** R^1 = OMe, R^2 = X = H; **8** R = Cl, **9** R = Br, **10** R = 1,3-dioxolan-2-yl; **11** R^1 = X = OMe, R^2 = H, R = Cl; **12** R^1 = R^2 = H, X = R = Cl; **13-18** R^1 = R^2 = X = H; **13** R = Cl, **14** R = Br, **15** R = I, **16** R = COOH, **17** R = 1,3-dioxolan-2-yl, **18** R = 2-methyl-1,3-dioxolan-2-yl, **19** R = R^2 = Cl, R^1 = X = H,

20 R^1 = R^2 = X = H, R = 

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Analysis of the ^{1}H NMR spectra of the 2,1-benzisoxazoles **1-10** leads not only to confirmation of the structure of the synthesized compounds but also to an unambiguous assignment of the proton signals. A special feature of these compounds is the occurrence of a 4-substituted phenyl substituent at the 3 position of the anthranil system. The protons of this benzene ring occur as two doublets with *ortho* constants since they contain in the para position either chlorine (compounds **1-6**), methyl (compound **7**), or a methoxy group (compounds **8-10**).

The chief feature of the ^{1}H NMR spectra of the studied compounds **1-20** (see Table 1) is the large difference in the chemical shift values for the H(4), H(6), and H(7) protons in the 2,1-benzisoxazole system when compared with the aromatic protons of the 4-R-C_6H_4 groups in position 3.

The signal which appears as a doublet with a *meta* constant is assigned to the H(4) proton [7] and is found at lowest field for all of the compounds considered. The signal for the H(6) proton appears as a double doublet with an *ortho* constant and has the lowest value chemical shift. Only for anthranil **4** (see Table 1) are the chemical shift values for the H(6) and H(7) protons coincident due to the electronic effect of the aldehyde group substituent in the 5 position. The doublet with an *ortho* constant in the ^{1}H NMR spectrum is assigned as the H(7) proton [7] and, for compounds **1-10**, has almost the same value (7.54-7.72 ppm). It is intermediate in value among the aromatic protons of the anthranil ring.

There is a marked effect of the 2,1-benzisoxazole ring on the position of the proton signals of the benzene ring (Ar') (the substituent in position 3) and this is equivalent to the effect of a modest electron-acceptor group [8]. One of the doublets from the H(2') and H(6') protons is found in an *ortho* position to the 2,1-benzisoxazole residue and is shifted to low field whereas the other doublet for H(3') and H(5') protons is at higher field. Not only the 2,1-benzisoxazole but also a substituent in the 5 position affects the position of these proton signals. Hence, for compound **4**, the chemical shift values for the Ar' protons are increased when compared with other anthranils.

Specific singlets are observed in the ^{1}H NMR spectra of the compounds studied from aliphatic groups for products which contain dioxolane rings (δ 3.8-4.12), and methyl (δ 1.63-2.45) or methoxy groups (δ 3.75-3.9) (compounds **5-11**).

Compound **11** shows the effect of two methoxy groups in the aryl substituent on the chemical shifts of the aromatic protons in the 2,1-benzisoxazole system such that the δ values for H(4), H(6), and H(7) are decreased and the difference in the chemical shift values between them is also decreased. The introduction of two substituents into Ar' changes the ^{1}H NMR spectrum to an ABC three spin system (Table 1).

The multiplicity of the aromatic protons signals (Ar') is increased for product **12** since the chlorine atom is found in a *meta* and not *para* position to the heteroaromatic ring.

Compounds **13-20** contain a phenyl substituent at position 3. This complicates the ^{1}H NMR spectrum somewhat and a more complex aromatic proton signal system (Ar') is found in place of the two doublets with *ortho* constants.

The electronic effect of the 2,1-benzisoxazole system on the position of the proton signals of the aryl substituent in position 3 is retained in all of the anthranils studied.

Hence by studying the ^{1}H NMR spectroscopic parameters for compounds **1-20** we conclude that structural changes lead to a marked difference (up to 1.15 ppm) in the chemical shifts of the proton signals. Informative ^{1}H NMR spectra of the anthranils investigated have the following general features. To low field with the highest chemical shift value is H(4) as a double doublet with a *meta* constant while the lowest value is for the H(6) double doublet with an *ortho* constant. The doublet with an *ortho* constant for H(7) occupies an intermediate position amongst the aromatic protons. The effect of the anthranil system is equivalent to a modest electron-acceptor group.

TABLE 1. ^{1}H NMR Spectra of the Anthranils in DMSO-d_6

Compound	Proton chemical shifts, δ, ppm (*J*, Hz)			
	H(4), d	H(6), dd	H(7), d	other signals
1	2	3	4	5
1	8.1 (J_{4-6} = 2.8, J_{4-7} = 1.2)	7.3 (J_{6-4} = 2.8, J_{6-7} = 8.9)	7.7 (J_{7-4} = 1.2, J_{7-6} = 8.9)	8.1 (2H, d, $J_{2'-3'}$ = 8.3, H-2',6'); 7.6 (2H, d, $J_{5'-6'}$ = 8.3, H-3',5')
2	8.30(J_{4-6} = 2.1, J_{4-7} = 1.5)	7.4 (J_{6-4} = 2.1, J_{6-7} = 8.3)	7.6 (J_{7-4} = 1.5, J_{7-6} = 8.8)	8.1 (2H, d, $J_{2'-3}$= 8.8, H-2',6'); 7.6 (2H, d, $J_{5'-6'}$ = 8.8, H-3',5')
3	8.5 (J_{4-6} = 2.9, J_{4-7} = 1.4)	7.5 (J_{6-4} = 2.9, J_{6-7} = 8.3)	7.6 (J_{7-4} = 1.4, J_{7-6} = 8.3)	8.1 (2H, d, $J_{2'-3'}$ = 9.3, H-2',6'); 7.6 (2H, d, $J_{5'-6'}$ = 9.3, H-3',5')
4	8.9 (J_{4-6} = 2.1, J_{4-7} = 1.2)	7.7 (J_{6-4} = 2.1, J_{6-7} = 8.7)	7.7 (J_{7-4} = 1.2, J_{7-6} = 8.7)	8.2 (2H, d, $J_{2'-3'}$ = 8.7, H-2',6'); 7.7 (2H, d, $J_{5'-6'}$ = 8.7, H-3',5')
5	8.0 (J_{4-6} = 2.7, J_{4-7} = 1.4)	7.4 (J_{6-4} = 2.7, J_{6-7} = 9.5)	7.6 (J_{7-4} = 1.4, J_{7-6} = 9.5)	8.1 (2H, d, $J_{2'-3'}$ = 8.2, H-2',6'); 7.6 (2H, d, $J_{5'-6'}$ = 8.2, H-3',5'); 5.8 (1H, s, CH); 4.0-4.1 (4H, m, CH_2O)
6	7.9 (J_{4-6} = 2.7, J_{4-7} = 1.4)	7.4 (J_{6-4} = 2.7, J_{6-7} = 9.5)	7.6 (J_{7-4} = 1.4, J_{7-6} = 9.5)	8.0 (2H, d, $J_{2'-3'}$ = 8.2, H-2',6'); 7.6 (2H, d, $J_{5'-6'}$ = 8.2, H-3',5'); 3.8-4.0 (4H, m, CH_2O); 1.63 (3H, s, CH_3)
7	8.1 (J_{4-6} = 2.8, J_{4-7} = 1.3)	7.3 (J_{6-4} = 2.8, J_{6-7} = 8.9)	7.7 (J_{7-4} = 1.3, J_{7-6} = 8.9)	7.9 (2H, d, $J_{2'-3'}$ = 8.3, H-2',6'); 7.4 (2H, d, $J_{5'-6'}$ = 8.3, H-3',5'); 2.4 (3H, s, CH_3)
8	7.9 (J_{4-6} = 2.6, J_{4-7} = 1.0)	7.2 (J_{6-4} = 2.6, J_{6-7} = 10.4)	7.5 (J_{7-4} = 1.0, J_{7-6} = 10.4)	7.9 (2H, d, $J_{2'-3'}$ = 8.8, H-2',6'); 7.1 (2H, d, $J_{5'-6'}$ = 8.8, H-3',5'); 3.7 (3H, s, OCH_3)
9	8.2 (J_{4-6} = 1.3, J_{4-7} = 1.0)	7.4 (J_{6-4} = 1.3, J_{6-7} = 8.5)	7.6 (J_{7-4} = 1.0, J_{7-6} = 8.5)	8.0 (2H, d, $J_{2'-3'}$ = 8.3, H-2',6'); 7.1 (2H, d, $J_{5'-6'}$ = 8.3, H-3',5'); 3.9 (3H, s, OCH_3)

TABLE 1 (continued)

1	2	3	4	5
10	7.9 ($J_{4\text{-}6}$ = 2.7, $J_{4\text{-}7}$ = 1.4)	7.3 ($J_{6\text{-}4}$ = 2.7, $J_{6\text{-}7}$ = 10.0)	7.5 ($J_{7\text{-}4}$ = 1.4, $J_{7\text{-}6}$ = 10.0)	7.9 (2H, d, $J_{2'\text{-}3'}$ = 10.0, H-2',6'); 7.6 (2H, d, $J_{5'\text{-}6'}$ = 10.0, H-3',5'); 5.7 (1H, s, CH); 3.9-4.1 (4H, m, CH_2O); 2.4 (3H, s, OCH_3)
11	7.9 ($J_{4\text{-}6}$ = 1.2, $J_{4\text{-}7}$ = 0.6)	7.6 ($J_{6\text{-}4}$ = 1.2, $J_{6\text{-}7}$ = 8.3)	7.5 ($J_{7\text{-}4}$ = 0.6, $J_{7\text{-}6}$ = 8.3)	7.4 (1H, d, $J_{2'\text{-}6'}$ = 2.1, $J_{2'\text{-}5'}$ = 0.6, H-2'); 7.2 (1H, dd, $J_{6'\text{-}2'}$ = 2.1, $J_{6'\text{-}5'}$ = 8.3, H-6'); 7.0 (1H, d, $J_{5'\text{-}2'}$ = 0.6, $J_{5'\text{-}6'}$ = 8.3, H-5')
12	8.2 ($J_{4\text{-}6}$ = 3.0, $J_{4\text{-}7}$ = 2.0)	7.4 ($J_{6\text{-}4}$ = 3.0, $J_{6\text{-}7}$ = 9.3)	7.7 ($J_{7\text{-}4}$ = 2.0, $J_{7\text{-}6}$ = 9.3)	8.1 (2H, m, $J_{2'\text{-}6'}$ = $J_{2'\text{-}4'}$ = 3.0, $J_{5'\text{-}2'}$ = 1.0, $J_{6'\text{-}5'}$ = 9.2, $J_{6'\text{-}2'}$ = $J_{6'\text{-}4'}$ = 3.0, H-2',6'); 7.6 (2H, m, $J_{5'\text{-}4'}$ = 9.2, $J_{5'\text{-}2'}$ = 1.0, H-5',4')
13	8.1 ($J_{4\text{-}6}$ = 2.8, $J_{4\text{-}7}$ = 1.3)	7.3 ($J_{6\text{-}4}$ = 2.8, $J_{6\text{-}7}$ = 8.9)	7.7 ($J_{7\text{-}4}$ = 1.3, $J_{7\text{-}6}$ = 8.9)	8.1 (2H, dd, $J_{2'\text{-}3'}$ = 7.8, H-2',6'); 7.6 (3H, m, $J_{5'\text{-}6'}$ = $J_{5'\text{-}4'}$ = 7.8, H-3',5',4')
14	8.3 ($J_{4\text{-}6}$ = 2.2, $J_{4\text{-}7}$ = 1.2)	7.4 ($J_{6\text{-}4}$ = 2.2, $J_{6\text{-}7}$ = 8.3)	7.6 ($J_{7\text{-}4}$ = 1.2, $J_{7\text{-}6}$ = 8.3)	8.1 (2H, dd, $J_{2'\text{-}3'}$ = 8.9, H-2',6'); 7.6 (3H, m, $J_{5'\text{-}6'}$ = $J_{5'\text{-}4'}$ = 8.9, H-3',5',4')
15	8.5 ($J_{4\text{-}6}$ = 2.7, $J_{4\text{-}7}$ = 1.3)	7.5 ($J_{6\text{-}4}$ = 2.7, $J_{6\text{-}7}$ = 8.0)	7.6 ($J_{7\text{-}4}$ = 1.3, $J_{7\text{-}6}$ = 8.0)	8.1 (2H, dd, $J_{2'\text{-}3'}$ = 7.8, H-2',6'); 7.6 (3H, m, $J_{5'\text{-}6'}$ = $J_{5'\text{-}4'}$ = 7.8, H-3',5',4')
16	8.6 ($J_{4\text{-}6}$ = 3.0, $J_{4\text{-}7}$ = 1.2)	7.6 ($J_{6\text{-}4}$ = 3.0, $J_{6\text{-}7}$ = 9.0)	7.8 ($J_{7\text{-}4}$ = 1.2, $J_{7\text{-}6}$ = 9.0)	8.1 (2H, dd, $J_{2'\text{-}3'}$ = 8.3, H-2',6'); 7.6 (3H, m, $J_{5'\text{-}6'}$ = $J_{5'\text{-}4'}$ = 8.3, H-3',5',4'); 13.0 (1H, s, COOH)
17	8.0 ($J_{4\text{-}6}$ = 3.0, $J_{4\text{-}7}$ = 1.2)	7.4 ($J_{6\text{-}4}$ = 3.0, $J_{6\text{-}7}$ = 8.6)	7.6 ($J_{7\text{-}4}$ = 1.2, $J_{7\text{-}6}$ = 8.6)	8.0 (2H, dd, $J_{2'\text{-}3'}$ = 8.4, H-2',6'); 7.6 (3H, m, $J_{5'\text{-}6'}$ = $J_{5'\text{-}4'}$ = 8.4, H-3',5',4'); 5.8 (1H, s, CH); 4.1-4.0 (4H, m, CH_2O)
18	8.0 ($J_{4\text{-}6}$ = 3.0, $J_{4\text{-}7}$ = 1.2)	7.4 ($J_{6\text{-}4}$ = 3.0, $J_{6\text{-}7}$ = 8.6)	7.6 ($J_{7\text{-}4}$ = 1.2, $J_{7\text{-}6}$ = 8.6)	8.0 (2H, dd, $J_{2'\text{-}3'}$ = 8.3, H-2',6'); 7.6 (3H, m, $J_{5'\text{-}6'}$ = $J_{5'\text{-}4'}$ = 8.3, H-3',5',4'); 1.6 (3H, s, CH_3); 4.0-3.8 (4H, m, CH_2O)
19	8.4 ($J_{4\text{-}7}$ = 1.1)	—	8.0 ($J_{7\text{-}4}$ = 1.1)	8.1 (2H, dd, $J_{2'\text{-}3'}$ = 8.4, H-2',6'); 7.6 (3H, m, $J_{5'\text{-}6'}$ = $J_{5'\text{-}4'}$ = 8.4, H-3',5',4')
20	8.3 ($J_{4\text{-}6}$ = 2.2, $J_{4\text{-}7}$ = 1.2)	7.6 ($J_{6\text{-}4}$ = 2.2, $J_{6\text{-}7}$ = 9.0)	7.4 ($J_{7\text{-}4}$ = 1.2, $J_{7\text{-}6}$ = 9.0)	8.0 (2H, dd, $J_{2'\text{-}3'}$ = 8.4, H-2',6'); 7.6 (3H, m, $J_{5'\text{-}6'}$ = $J_{5'\text{-}4'}$ = 8.4, H-3',5',4'); 7.4-7.5 (5H, m, H-2'',3'',4'',5'',6'')

EXPERIMENTAL

The 2,1-benzisoxazoles (anthranils) were prepared by the method in [2]. ^{1}H NMR spectra were taken on a Bruker AC-300 spectrometer (300 MHz) using DMSO-d_6 and relative to HMDS.

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