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The double ring closure of *N*-(2-hydroxybenzyl)anthranilic acids **1** with acetic anhydride or its acyclic analogous (RCH₂CO)₂O **2b** and **2e** lead to the formation of novel 12*H*-quino[2,1-*b*][1,3]benzoxazin-5-ones. The structure of the obtained compounds was proved with the use of their ir, mass, ¹H and ¹³C nmr spectra. Homo- and heteronuclear two-dimensional nmr experiments were performed to unambiguously assign all proton and carbon chemical shifts.

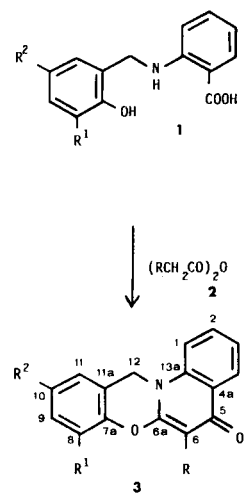
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To the best of our knowledge 12*H*-quino[2,1-*b*][1,3]benzoxazine was hitherto an unknown class of heterocycles as a whole, even if the same arrangement of two or three fused rings - including the 1,3-oxazine system with bridgehead nitrogen - occurs in several, differently hydrogenated, 1-oxaquinolizine systems [2] and their benzo[*b*] derivatives [3]. Moreover the synthesis of four diastereoisomeric 6,7*a*,8,9,10,11,11*a*,11*b*,12,13-decahydro-[1,2-*c*][1,3]benzoxazines was described [4].

In connection with our work on the chemical behaviour of Mannich products obtained with the use of anthranilic acid as the amine component [5], we have investigated the reaction of *N*-(2-hydroxybenzyl)anthranilic acids **1** [5*a*] with acetic anhydride or its acyclic analogous (RCH₂CO)₂O **2b** and **2e**. The reaction occurs rapidly in the range 140-170° using the specific anhydride as reaction solvent, and gives 12*H*-quino[2,1-*b*][1,3]benzoxazin-5-ones **3** in satisfying yields (>50%). Most likely the formation of **3** takes place *via* the acylation of **1** and subsequent double ring closure. The reaction provides further evidence of the usability of *N*-(2-hydroxybenzyl)anthranilic acids **1** to build up fused heterocyclic systems [5*c*] by easy synthetic operations.

The ir spectra of the 12*H*-quino[2,1-*b*][1,3]benzoxazin-5-ones **3** are characterized by several strong bands in the 1640-1555 cm⁻¹ region, where the highest frequency bond cannot be unambiguously assigned to the carbonyl stretching vibration, owing to the considerable degree of mixing of the ring and carbonyl modes observed for many systems of the same kind, such as 4-pyridones and -quinolones [6]. The particularly low carbonyl frequencies in **3** are explained in terms of the very enhanced resonance which results from delocalization of the nitrogen lone pair electrons towards the carbonyl oxygen atom and predictable competition of the benzoxazine oxygen lone pair in the same donation.

The mass spectrum of **3g** shows the molecular ion as the base peak at *m/z* 263, while the molecular ion of **3e** has 58% intensity in the normalized spectrum.



	R	R ¹	R ²
a	H	H	H
b	Cl	H	H
c	H	Me ¹⁵	Cl
d	Cl	Me	Cl
e	Me ¹⁴	H	Me ¹⁶
f	H	Me	Me
g	H	H	Me

The ¹H nmr parameters of compounds **3** are reported in Table I. While the identification of H-6, H₂-12 and methyl proton signals are straightforward, the interpretation of the aromatic portions of the spectra deserves special comments. The 500 and 250 MHz spectra of **3e** and **3g** clearly show two separate moieties of aromatic signals, the higher field part due to H-8, H-9, and H-11 resonances, and four lower field multiplets, coming from H-1 to H-4. The H-8, H-9, and H-11 absorptions were individually assigned on the basis of their multiplicities and heteronuclear 2D experiments [7*a*] whereby the correlation map of proton *vs.* carbon chemical shifts were obtained: the signals at 115.9, 130.2 (130.3), and 126.3 ppm in **3e** and **3g** are assigned to

Table I

¹H NMR Spectroscopic Data of 12*H*-Quino[2,1-*b*]1,3]benzoxazin-5-ones **3**

	3a (250 MHz)	3b (60 MHz)	3c (200 MHz)	3d (200 MHz)	3e (500 MHz)	3f (500 MHz)	3g (250 MHz)
δ (ppm) H-1	7.55		7.52	7.54	7.47	7.54	7.51
H-2	7.70		7.72	7.75	7.61	7.70	7.69
H-3	7.40		7.43	7.47	7.29	7.42	7.38
H-4	8.41	8.2-6.7 (ArH)	8.45	8.54	8.37	8.46	8.42
H-8	7.19				7.07		7.05
H-9	7.24		7.18	7.20	7.13	7.00	7.15
H-10	7.38						
H-11	7.34		7.13	7.17	7.08	6.91	7.10
H-6	6.07		6.13			6.12	6.02
H ₂ -12	5.17	5.07	5.14	5.23	5.09	5.11	5.09
H ₂ -14					2.17		
H ₂ -15			2.37	2.47		2.30	
H ₂ -16					2.35	2.33	2.37
J _{1,2} (Hz)	8.63		8.3	8.4	9.0	8.0	8.13
J _{1,3}	0.52						0.63
J _{2,3}	7.11		7.0	7.5	7.2	7.7	7.08
J _{2,4}	1.51		1.6		1.5	2.0	1.59
J _{3,4}	8.13		7.7	8.0	8.0	8.2	7.68
J _{8,9}	9.07				8.0		7.90
J _{8,10}	0.57						
J _{9,10}	8.88						
J _{9,11}	1.00						2.69
J _{10,11}	7.80						

Table II

¹³C Chemical Shift Data (δ, ppm) for 12*H*-Quino[2,1-*b*]1,3]benzoxazin-5-ones **3**

	3a (63 MHz)	3c (126 MHz)	3e (126 MHz)	3f (126 MHz)	3g (63 MHz)
C-1	114.08	114.04	113.73	114.09	114.00
C-2	132.10	134.22	131.60	132.06	131.95
C-3	124.19	124.50	123.74	124.20	124.05
C-4	126.72	127.00	126.66	126.79	126.71
C-4a	114.92	116.08	114.64	114.25	114.50
C-5	178.15	178.25	177.39	178.20	178.05
C-6	94.81	94.92	102.76	94.75	94.71
C-6a	138.19	138.04	137.02	138.20	138.24
C-7a	154.21	155.65	151.36	154.70	154.32
C-8	116.27	126.31	115.90	125.65	115.96
C-9	129.73	130.98	130.20	131.76	130.31
C-10	124.80	129.45	134.54	134.09	134.54
C-11	126.29	123.43	126.34	123.78	126.37
C-11a	126.29	128.10	124.47	126.32	126.44
C-12	43.45	43.25	43.79	43.59	43.46
C-13a	146.76	143.78	144.79	143.10	144.67
C-14		8.29			
C-15		15.31		15.18	
C-16			20.79	20.75	20.79

C-8, C-9, and C-11 respectively (Table II) and take into account the well known substituent effects in benzene derivatives [8]. Then the nmr parameters of aromatic protons were fully calculated and assigned for all compounds **3**, considering that the H-4 four line resonance is always the lowest field absorption, deshielded to 8.4-8.5 ppm by

the adjacent carbonyl group. The computer simulation of the aromatic part of **3a** and **3g** ¹H nmr spectra (250 MHz) was carried out by the LAOCN3 program [9]. The thus calculated vicinal and long-range coupling constants are shown in Table I, while the other reported coupling constants are directly read on the spectra. A slight long-range coupling between H-1 and H₂-12 was verified in **3a** by suitable decoupling experiments. All proton resonance parameters were finally confirmed by a COSY experiment (2D) on **3e** [7b].

Spectral editing by spin-echo modulation and DEPT experiments [7c] were used for determining the multiplicities of carbon signals in ¹³C nmr spectra of **3** at 63 or 126 MHz (Table II). Definitive assignments were achieved by heteronuclear 2D experiments performed on **3c, e, f**, and are in line with ¹³C nmr parameters of methyl anthranilate [10a].

Noteworthy in the assignment of the structure was the highest field carbon resonance at 8.29 ppm in **3e**, due to C-14: an analogous chemical shift (8.2 ppm) was observed in 2,5-dimethoxy-6-isopropyl-3-methyl-1,4-benzoquinone [10b] for the 3-methyl group, whose carbon atom shows a chemical environment like that of C-14 in **3e**.

Spectral data were all unambiguously consistent with the structures attributed to compounds **3**. A broad effectiveness of the synthesis here reported is suggested by its occurrence in the presence of **2b** and **2e**, besides **2a**, owing to the opposite electronic effects of methyl- and chloro-substituents in the anhydride system.

EXPERIMENTAL

Melting points were determined with a Kofler apparatus and are uncorrected. Analyses were performed on a Carlo Erba Model 1106 elemental analyzer, taking the right precautions because of the hygroscopicity of **3**. The ir spectra (nujol mulls) were recorded on a Perkin Elmer 682 spectrophotometer. The nmr spectra were obtained in deuteriochloroform with Varian EM 360 A, Bruker AM-200, 250, 500 spectrometers, using tetramethylsilane as an internal standard. Mass spectra were scanned with a Varian MAT CH7 spectrometer at 70 eV.

General Procedure for the Preparation of 12*H*-Quino[2,1-*b*][1,3]benzoxazin-5-ones **3**.

The compound **1** (8 mmoles) [**5a**], suspended in the anhydride **2** (100 mmoles), was warmed at 140-170° for two hours: the solid **1** was slowly dissolved. After cooling to the laboratory temperature, the reaction mixture was diluted with chloroform (50 ml), added to water (50 ml), and neutralized by adding solid sodium bicarbonate in small portions under vigorous stirring. The organic layer was separated, washed with water, dried, and evaporated under reduced pressure. The residue was chromatographed over silica gel column (Kieselgel S, 0.063-0.2 mm, Riedel-de Haën) eluting with diethyl ether, then with a gradient of diethyl ether and acetone (20% acetone at most).

12*H*-Quino[2,1-*b*][1,3]benzoxazin-5-one (**3a**).

This compound had mp 261-263°; ir: 1640, 1628, 1613, 1558, 1497, 1280 cm⁻¹.

Anal. Calcd. for C₁₆H₁₁NO₂: C, 77.10; H, 4.45; N, 5.62. Found: C, 77.11; H, 4.46; N, 5.44.

6-Chloro-12*H*-quino[2,1-*b*][1,3]benzoxazin-5-one (**3b**).

This compound had mp 240-242°; ir: 1622, 1600, 1540, 1492, 1275, 1220 cm⁻¹.

Anal. Calcd. for C₁₇H₁₀ClNO₂: C, 67.74; H, 3.55; N, 4.94. Found: C, 67.50; H, 3.80; N, 4.89.

10-Chloro-8-methyl-12*H*-quino[2,1-*b*][1,3]benzoxazin-5-one (**3c**).

This compound had mp 273-275°; ir: 1640, 1630, 1615, 1555, 1490, 1278 cm⁻¹.

Anal. Calcd. for C₁₇H₁₂ClNO₂: C, 68.58; H, 4.06; Cl, 11.91; N, 4.70. Found: C, 68.43; H, 4.30; Cl, 12.07; N, 4.55.

6,10-Dichloro-8-methyl-12*H*-quino[2,1-*b*][1,3]benzoxazin-5-one (**3d**).

This compound had mp 298-300°; ir: 1640, 1630, 1610, 1548, 1510, 1270 cm⁻¹.

Anal. Calcd. for C₁₇H₁₁Cl₂NO₂: C, 61.47; H, 3.34; N, 4.22. Found: C, 61.45; H, 3.34; N, 4.13.

6,10-Dimethyl-12*H*-quino[2,1-*b*][1,3]benzoxazin-5-one (**3e**).

This compound had mp 256-258°; ir: 1640, 1630, 1608, 1545, 1499, 1278 cm⁻¹; ms: *m/z* (% relative intensity) 277 (58, M⁺), 248 (27), 149 (35), 137 (39), 118 (48), 92 (45), 86 (27), 84 (32), 71 (43), 69 (33), 57 (100), 55 (39).

Anal. Calcd. for C₁₈H₁₅NO₂: C, 77.96; H, 5.45; N, 5.05; Found: C, 78.17; H, 5.67; N, 5.33.

8,10-Dimethyl-12*H*-quino[2,1-*b*][1,3]benzoxazin-5-one (**3f**).

This compound had mp 237-239°; ir: 1640, 1630, 1612, 1557, 1495, 1275 cm⁻¹.

Anal. Calcd. for C₁₈H₁₅NO₂: C, 77.96; H, 5.45; N, 5.05. Found: C, 77.67; H, 5.61; N, 5.30.

10-Methyl-12*H*-quino[2,1-*b*][1,3]benzoxazin-5-one (**3g**).

This compound had mp 285-287°; ir: 1640, 1630, 1610, 1560, 1510, 1282 cm⁻¹; ms: *m/z* (% relative intensity) 263 (100, M⁺), 262 (36), 246 (12), 235 (20), 234 (17).

Anal. Calcd. for C₁₇H₁₃NO₂: C, 77.55; H, 4.98; N, 5.32. Found: C, 77.54; H, 5.29; N, 5.60.

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