Identification of the Nitrosation Reaction Products of Alkyl Esters of 1,2-Benzisoxazole-3-acetic Acid by Chemical and Crystallographic Methods (1)

Mario Giannella*

Dipartimento di Scienze Chimiche, Universitá di Camerino, via S. Agostino, 1, 62032 Camerino (MC), Italy

Fulvio Gualtieri

Istituto di Chimica Farmaceutica, Universitá di Firenze, 50121 Firenze, Italy

Walter Fedeli

Istituto di Chimica, Universitá dell'Aquila, 67100 L'Aquila, Italy

Silvio Cerrini and Enrico Gavuzzo

Istituto di Strutturistica Chimica del CNR, 00016 Monterotondo Stazione, Roma, Italy

Received June 10, 1982

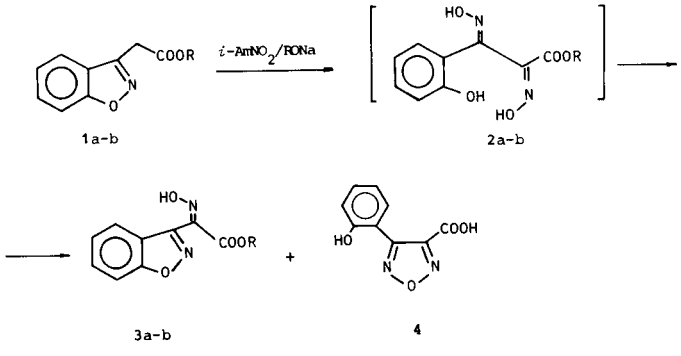
The reaction between methyl or ethyl esters of 1,2-benzisoxazole-3-acetic acid and *iso*-amyl nitrite is reported. The main product is identified as 4-(2'-hydroxyphenyl)furazan-3-carboxylic acid (**4**) by chemical and X-ray crystal structure analyses. The synthesis of esters of *E*- and *Z*-α-(hydroxyimino)-1,2-benzisoxazole-3-acetic acid is also reported.

J. Heterocyclic Chem., **20**, 385 (1983).

In the course of the research on indole isosters with a 1,2-benzisoxazole nucleus (2-5), from which could be obtained biologically interesting compounds (6), esters of *E*-and *Z*-α-(hydroxyimino)-1,2-benzisoxazole-3-acetic acid were required.

The nitrosation of alkyl esters of 1,2-benzisoxazole-3-acetic acid (**1**) (7) could be achieved in low yield only when drastic conditions were used. Thus, the reaction between methyl ester **1a** and *iso*-amyl nitrite in the presence of sodium methylate afforded the expected *E*-α-(hydroxyimino)-1,2-benzisoxazole-3-acetic acid methyl ester (**3a**) in low yield, the main product (80-85% yield) being the acid **4** which was independent from the nature of the ester as confirmed by the reaction of the ethyl ester (**1b**). Compound **4** was identified as 4-(2'-hydroxyphenyl)furazan-3-carboxylic acid and could be obtained through the dioxyme **2** (Scheme 1) and this agrees with the previously reported rearrangement of isoxazoles in basic medium (8).

Scheme 1



Scheme 2

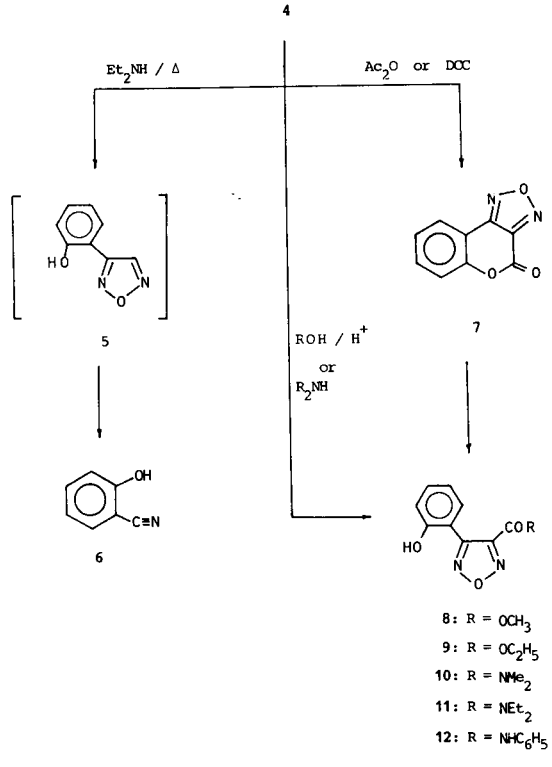
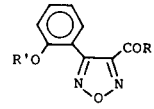


Table I

Analytical and Spectroscopical Data



N°	R	R'	Mp °C (a)	Molecular Formula (M.W.)	Elemental Analysis Calcd. (Found) C	H	N	NMR (b)	IR (nujol, cm^{-1}) (c)
4	OH	H	136-138 (A)	$C_9H_6N_2O_4$ (206.15)	52.43 (52.53)	2.93 (3.18)	13.59 (13.43)	(DMSO-d_6): 7.00 (m, 2H, aromatic), 7.46 (m, 2H, aromatic), 10.66 (bs, 2H, exchangeable)	3400, 2650, 2550, 1710, 1600
8	OCH_3	H	108-110 (B)	$C_{10}H_8N_2O_4$ (220.18)	54.55 (54.58)	3.66 (3.48)	12.72 (12.69)	(deuteriochloroform): 4.00 (s, 3H, CH_3), 7.03 (m, 3H, aromatic and -OH exchangeable), 7.40 (m, 1H, aromatic), 7.73 (m, 1H, aromatic)	3425, 1730, 1605,
9	OC_2H_5	H	52-54 (C)	$C_{11}H_{10}N_2O_4$ (234.21)	56.41 (56.23)	4.30 (4.49)	11.96 (12.01)	(deuteriochloroform): 1.35 (t, 3H, CH_3), 4.44 (q, 2H,CH_2), 7.05 (m, 3H, aromatic and -OH exchangeable), 7.41 (m, 1H, aromatic), 7.69 (m, 1H, aromatic)	3380, 1720, 1615,
10	NMe_2	H	172-174 (D)	$C_{11}H_{11}N_3O_3$ (233.22)	56.65 (56.43)	4.75 (4.81)	18.02 (18.26)	(DMSO-d_6): 3.01 (s, 6H, NMe_2), 7.02 (m, 2H, aromatic), 7.40 (m, 1H, aromatic), 7.58 (m, 1H, aromatic), 10.44 (s, 1H, -OH exchangeable)	3050, 2650, 2550, 1625, 1600
11	NEt_2	H	157-160 (D)	$C_{13}H_{15}N_3O_3$ (261.27)	59.76 (59.56)	5.79 (6.01)	16.08 (15.96)	(DMSO-d_6): 1.18 (t, 6, $2\times CH_3$), 3.40 (q, 4, $2\times CH_2$), 7.00 (m, 2H, aromatic), 7.46 (m, 2H, aromatic), 10.33 (s, 1H, -OH exchangeable)	3070, 2680, 2550, 1625, 1605
12	NHC_6H_5	H	161-162 (D)	$C_{15}H_{11}N_3O_3$ (281.26)	64.05 (63.91)	3.94 (4.07)	14.94 (14.67)	(DMSO-d_6): 6.90-8.00 (m, 9H, aromatic), 10.50 and 10.75 (bs, 2H, exchangeable)	3300. 1680, 1610,
19	OCH_3	$COCH_3$	—	$C_{12}H_{10}N_2O_5$ (262.22)	55.96 (55.17)	3.84 (3.83)	10.68 (10.76)	—	1760, 1730, 1610,
20	OC_2H_5	$COCH_3$	—	$C_{13}H_{12}N_2O_5$ (276.24)	56.52 (56.78)	4.38 (4.15)	10.14 (10.31)	—	1760, 1725, 1605,
21	OCH_3	CH_3	49-50 (B)	$C_{11}H_{10}N_2O_4$ (234.21)	56.41 (56.33)	4.30 (4.51)	11.96 (12.11)	(deuteriochloroform): 3.71 and 3.84 (s, 6H, $2\times CH_3$), 7.00 (m, 2H, aromatic), 7.48 (m, 2H, aromatic)	1730, 1600,

(a) Recrystallization Solvent: (A) = benzene; (B) = benzene-*n*-hexane; (C) = *n*-hexane; (D) = ethanol-water. (b) Chemical shifts in δ units. (c) Unless otherwise specified, spectra were determined in nujol mull.

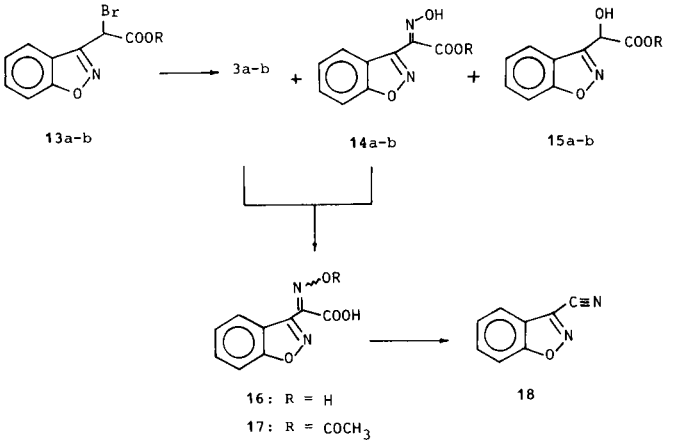
Similarly, treatment of esters **3** and **14** or of acid **16** with sodium hydroxide gave compound **4** as well. The structure of **4** has been confirmed by X-ray diffraction of its methyl ester (**8**) (see corresponding section) and by chemical considerations. In fact the decarboxylation of **4** in diethylamine gave 2-hydroxybenzonitrile (**6**), possibly through the intermediate 3-(2'-hydroxyphenyl)furazane (**5**) which, according to the (9a-b) references, is very unstable and thus could not be completely characterized (Scheme 2).

Upon treatment with acetic anhydride or other dehydrating agents, compound **4** gave the 4*H*-furazan[3,4-*c*][1]-benzopyran-4-one (**7**) whose structure was confirmed by the ir spectrum (ν CO 1790 cm^{-1}) (10) and mass spectrometry (MW m/e 188). Compound **7** can be easily opened by a number of nucleophilic reagents to the corresponding derivatives of acid **4** (**8-12**).

The structure of *E*-α-(hydroxyimino)-1,2-benzisoxazole-3-acetic acid methyl ester **3a** was confirmed through the

reaction of the methyl ester of α-bromo-1,2-benzisoxazole-3-acetic acid (**13a**) (11) with sodium nitrite (12) (Scheme 3).

Scheme 3



The methyl ester of α-hydroxy-1,2-benzisoxazole-3-acetic acid (**15a**) was the main reaction product together with two other compounds one of which was identical to the previously referred methyl ester **3a**. The other compound **14a** could be isomerized to a mixture containing both **3a** and **14a** (in a 3:2 ratio) by acids, thus showing that the two products are *E* and *Z* isomers of α-(hydroxyimino)-1,2-benzisoxazole-3-acetic acid methyl ester.

The structure of the two isomers was identified on the basis of their ir and nmr spectra, since chemical reactions could not be used for the easy isomerization of the *E* and *Z* forms. In fact, the reaction of **3a-b** or **14a-b** with 2*N* hydrochloric acid gave only a mixture of the two isomeric α-(hydroxyimino)-1,2-benzisoxazole-3-acetic acids (**16**). As a consequence, the formation of nitrile **18** (13) cannot help in establishing the structure of the two isomers. On the other hand, the esters of the *Z* series (**14a-b**) show a bonded hydroxyl group in the ir spectrum (0.5% solution in chloroform), whereas a free -OH is present in the spectra of the corresponding *E* series (**3a-b**). Moreover the aromatic protons of compounds **14a-b** cluster between 7.82 and 6.89 ppm while compounds **3a-b** show an aromatic proton at lower field (about 8.00 ppm) due to the deshielding effect of the hydroxyl *sin* to the phenyl group (14a-c).

X-Ray Crystal Structure of **8**.

Suitable single crystals for an X-ray structure analysis were obtained by slow evaporation from a benzene solution of compound **8**. The crystal data are the following: $C_{10}H_8N_2O_4$, M.W. = 220.18; monoclinic, space group $P2_1/c$ from systematic absences; a = 15.090 (9), b = 8.968 (6), c = 7.764 (4) Å, β = 97.70 (5) °, V = 1041 (1) Å^3, Z = 4, D_c = 1.40 g.cm.$^{-3}$, λ (Cu-K$_\alpha$) = 1.5418 Å. The intensities of 2300 independent reflections (θ max = 55.0°) were measured by θ-2θ scan technique on a Siemens automatic four-circle diffractometer. Owing to the poor quality of the crystal used for data collection, only 1155 reflections had $I > 3\sigma(I)$ and were used in the refinement. Lorentz and polarization factors, but no absorption and extinction corrections were applied [μ(Cu-K$_\alpha$) = 24.93 mm^{-1}]. The structure was solved by direct methods using MULTAN 78 programme (15). The final difference Fourier synthesis revealed acceptable atomic positions for all the hydrogen atoms. The structure was anisotropically refined by block-diagonal least-squares calculations for all the non-hydrogen atoms; the hydrogen atom parameters were kept fixed with isotropic thermal values assumed from the carrier atoms. The quantity minimized was $\Sigma w(|F_o| - |F_c|)^2$ where $w = (a + |F_o| + c|F_o|^2)^{-1}$ with a and c of the order of $2F_{o\,[min]}$ and $2/F_{o\,[max]}$ respectively. The final R and R_w are 0.095 and 0.139 respectively. All the calculations were carried out on the HP 1000 minicomputer (16) of the CNR Research Area of Rome and on the UNIVAC 1100/80 computer of the University of Rome. The molecular structure of **8** together with the numbering scheme adopted is shown in figure 1, its final atomic coordinates are given in Table III, and the bond distances and angles together with their standard deviations are in Table IV.

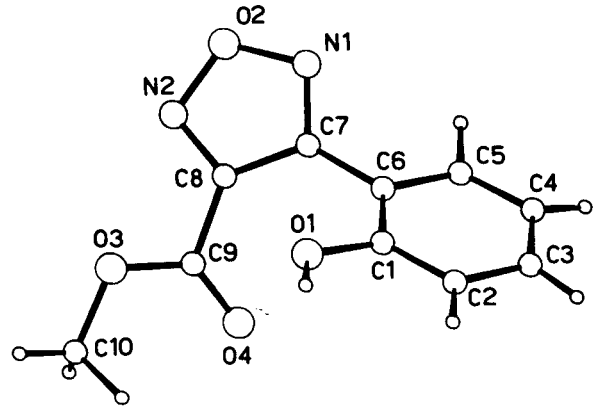


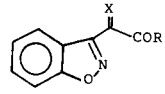
Figure 1. A perspective view of the molecule together with the atomic numbering scheme adopted.

Both aromatic rings are planar, with an average deviation from the least-squares plane of the phenylic cycle of 0.008 Å (maximum deviation = 0.016 Å for C(4)) and an average deviation of 0.005 Å (maximum deviation = 0.007 Å for C(7)) for the furazanic cycle. The rather short C(6)-C(7) bond distance (1.44 Å) might indicate conjugation between the rings, although the dihedral angle between them (47.8°) is appreciably different from zero.

The carbomethoxy group is planar with a maximum deviation of 0.004 Å from the best plane and the dihedral

Table II

Analytical and Spectroscopical Data



N°	R	X	Configuration	Rf (d)	Mp °C (a) or bp (mm)	Molecular Formula (MW)	Elemental Analysis Calcd. (Found) C	H	N	NMR (b)	IR (nujol, cm^{-1}) (c)
3a	OCH_3	NOH	*E*	0.264	137-138 (B)	$C_{10}H_8N_2O_4$ (220.18)	54.55 (54.71)	3.66 (3.70)	12.72 (12.68)	(deuteriochloroform): 4.07 (s, 3H, CH_3), 7.28-7.73 (m, 3H, aromatic), 8.11 (d, 1H, aromatic), 9.69 (sb, 1H, -OH exchangeable)	3170, 1740, 1610
3b	OC_2H_5	NOH	*E*	0.297	133-135 (A)	$C_{11}H_{10}N_2O_4$ (234.21)	56.41 (56.63)	4.30 (4.14)	11.96 (12.03)	(deuteriochloroform): 1.40 (t, 3H, CH_3), 4.50 (q, 2H, CH_2), 7.26-7.69 (m, 3H, aromatic), 8.05 (d, 1H, aromatic), 9.70 (sb, 1H, -OH exchangeable)	(chloroform) 3555, 3260, 1735, 1610; (0.5% chloroform), 3555 (-OH free)
13b	OC_2H_5	H,Br	—	—	135 (2)	$C_{11}H_{10}BrNO_3$ (284.11)	46.50 (46.55)	3.55 (3.71)	4.93 (4.82)	(deuteriochloroform): 1.28 (t, 3H, CH_3), 4.31 (q, 2H, CH_2), 5.84 (s, 1H, CH), 7.26-7.69 (m, 3H, aromatic), 8.03 (d, 1H, aromatic)	1730, 1600
14a	OCH_3	NOH	*Z*	0.165	118-120 (B)	$C_{10}H_8N_2O_4$ (220.18)	54.55 (54.67)	3.66 (3.73)	12.72 (12.58)	(deuteriochloroform): 4.02 (s, 3H, CH_3), 7.20-7.78 (m, 5H, aromatic and -OH exchangeable)	3200, 1735 1610
14b	OC_2H_5	NOH	*Z*	0.208	114-115 (B)	$C_{11}H_{10}N_2O_4$ (234.21)	56.41 (56.27)	4.30 (4.19)	11.96 (11.79)	(deuteriochloroform): 1.30 (t, 3H, CH_3), 4.38 (q, 2H, CH_2), 6.89-7.82 (m, 5H, aromatic and -OH exchangeable)	(chloroform) 3540, 3290, 1730, 1610; (0.5% chloroform) 3290 (OH bonded)
15a	OCH_3	H, OH	—	0.229	63 (B)	$C_{10}H_9NO_4$ (207.18)	57.97 (58.00)	4.38 (4.22)	6.76 (6.59)	(DMSO-d_6): 3.69 (s, 3H, CH_3), 5.76 (s, 1H, CH), 6.79 (sb, 1H, -OH exchangeable), 7.33-8.00 (m, 4H, aromatic)	3300, 1740 1610
15b	OC_2H_5	H, OH	—	0.284	90-92 (B)	$C_{11}H_{11}NO_4$ (221.21)	59.72 (60.01)	5.01 (5.16)	6.33 (6.25)	(deuteriochloroform): 1.21 (t, 3H, CH_3), 3.86 (sb, 1H, -OH exchangeable), 4.30 (q, 2H, CH_2), 5.70 (s, 1H, CH), 7.18-7.92 (s, 4H, aromatic)	3250, 1740 1610
16	OH	NOH	—	—	173-174 (E)	$C_9H_6N_2O_4$ (206.15)	52.43 (52.24)	2.93 (3.10)	13.59 (13.40)	(CD_3COCD_3): 6.10 (sb, 2H, -OH exchangeable), 7.38-7.82 (m, 4H, aromatic)	3350, 3150 1715
22	OC_2H_5	$NOCONHC_6H_5$	*E*	0.426	149-151 (E)	$C_{18}H_{15}N_3O_5$ (353.32)	61.19 (61.31)	4.28 (4.40)	11.89 (12.07)	(DMSO-d_6): 1.40 (t, 3H, CH_3), 4.56 (q, 2H, CH_2), 7.03-8.10 (m, 8H, aromatic), 8.26 (d, 1H, aromatic), 10.36 (s, 1H, NH exchangeable)	3300, 1740, 1730, 1610
23	OC_2H_5	$NOCONHC_6H_5$	*Z*	0.355	132-134 (F)	$C_{18}H_{15}N_3O_5$ (353.32)	61.19 (61.00)	4.28 (4.35)	11.89 (12.10)	(DMSO-d_6): 1.32 (t, 3H, CH_3), 4.48 (q, 2H, CH_2), 6.91-8.08 (m, 9H, aromatic), 10.20 (s, 1H, NH exchangeable)	3340, 1760 1720, 1610

24	OC_2H_5	$NOCH_3$	*E*	—	46-50 (B)	$C_{12}H_{12}N_2O_4$ (248.23)	58.06 (58.12)	4.87 (4.99)	11.29 (11.07)	(deuteriochloroform): 1.40 (t, 3H, CH_3), 4.18 (s, 3H, OCH_3), 4.48 (q, 2H, CH_2), 7.18-7.68 (m, 3H, aromatic), 8.11 (m, 1H, aromatic)	1750, 1620

(a), (b), (c) See corresponding footnotes at Table I; (A) = benzene; (B) = benzene-*n*-hexane; (C) = *n*-hexane; (D) = ethanol-water; (E) = ethyl acetate-petroleum ether; (F) = dichloromethane-petroleum ether. (d) Eluting system: cyclohexane-ethyl acetate 3:2.

angle between this plane and that of the five membered ring is 27.3°.

The molecular packing (Figure 2) is characterized by an intermolecular hydrogen bond of 2.77 Å between O(1) and O(4) atoms of glide related molecules. The H(01)...O(4) distance is 1.85 Å, the C(9)-O(4)...H(01) and C(9)-O(4)...O(1) angles are 166.2° and 160.5° respectively, the O(4)...H(01)-O(1) angle is 163.0° and the C(9)-O(4)...H(01)-O(1) dihedral angle is -15.58°. Finally there are no intermolecular contacts significantly shorter than the sum of the van der Waals radii.

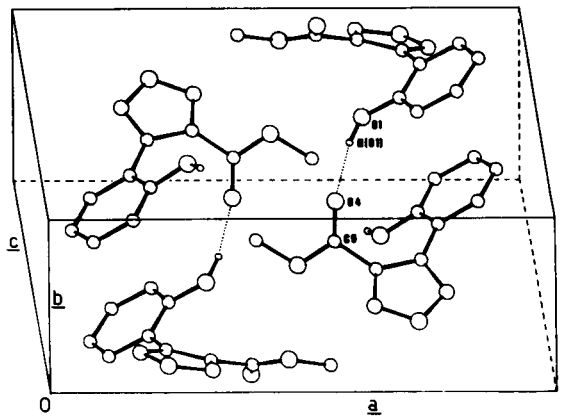


Figure 2. The crystal packing. Dashed lines represent hydrogen bonds.

EXPERIMENTAL

Melting points were determined on a Büchi SMP-20 apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer 297 instrument. The nmr spectra were obtained using a Varian EM-390 spectrometer with tetramethylsilane as internal standard. Mass spectra were recorded on a Varian MAT 711 spectrometer. The reactions were monitored by tlc silica gel plates and chromatographic separations were performed on silica gel column (Kieselgel 40, 0.063 to 0.200 mm; Merck), using cyclohexane-EtOAc 3:2 mixture as eluting system. Elemental analyses were determined on a Perkin-Elmer 240 analyser.

Reaction of 1,2-Benzisoxazole-3-acetic Acid Methyl Ester With *iso*-Amyl Nitrite.

Sodium methoxide (3.1 g of sodium in 100 ml of anhydrous methanol) was added to an ice cooled mixture of 1,2-benzisoxazole-3-acetic acid methyl ester (**1a**) (7.2 g) (7) and *iso*-amyl nitrite (5.4 g). The mixture was stirred at 0° for 4 hours; the yellow solid was then filtered, washed (ether), dissolved in a small amount of water, acidified with 2*N* hydrochloric acid and extracted with ether. Evaporation of the dried (sodium

Table III

Fractional coordinates with e.s.d.'s in parentheses and isotropic thermal parameter B. For the non-hydrogen atoms B is defined as $B_{eq} = 8\pi^2(U_1U_2U_3)^{1/3}$, where U_i are the mean-square displacements along the principle axes

	x	y	z	B (Å²)
C(1)	.7751(4)	.2239(7)	.6640(8)	3.0
C(2)	.8128(5)	.3613(8)	.7092(11)	4.1
C(3)	.8980(6)	.3641(12)	.8080(11)	5.0
C(4)	.9439(6)	.2345(14)	.8581(12)	6.2
C(5)	.9040(5)	.0990(10)	.8163(11)	4.5
C(6)	.8188(4)	.0919(7)	.7156(8)	2.9
C(7)	.7810(5)	-.0513(7)	.6640(8)	3.2
C(8)	.6923(5)	-.1085(7)	.6675(9)	3.3
C(9)	.6163(5)	-.0419(7)	.7438(8)	3.1
C(10)	.4607(5)	-.0397(15)	.7476(13)	6..1
N(1)	.8266(5)	-.1527(8)	.5942(10)	5.1
N(2)	.6847(5)	-.2444(8)	.6038(11)	5.7
O(1)	.6943(3)	.2127(5)	.5634(7)	4.0
O(2)	.7687(5)	-.2742(6)	.5568(10)	5.9
O(3)	.5385(3)	-.0957(7)	.6752(7)	4.5
O(4)	.6270(3)	.0474(5)	.8613(6)	3.5
H(C2)	.7795	.4568	.6716	4.7
H(C3)	.9191	.4640	.8422	6.2
H(C4)	.9991	.2457	.9385	6.3
H(C5)	.9400	-.0015	.8314	6.2
H1(C10)	.4042	-.0577	.6668	8.3
H2(C10)	.4553	-.0882	.8626	8.3
H3(C10)	.4700	.0909	.7700	8.3
H(O1)	.6656	.3000	.5133	4.7

Table IV

Bond distances (Å) and angles (°) between the non-hydrogen atoms with e.s.d.'s in parentheses

Bond distances		Bond angles	
C(1)-O(1)	1.361(8)	O(1)-C(1)-C(2)	121.2(6)
C(1)-C(2)	1.382(10)	O(1)-C(1)-C(6)	117.1(6)
C(1)-C(6)	1.388(9)	C(1)-C(6)-C(5)	118.8(7)
C(2)-C(3)	1.406(13)	C(1)-C(6)-C(7)	121.7(6)
C(3)-C(4)	1.381(16)	C(1)-C(2)-C(3)	118.0(7)
C(4)-C(5)	1.376(15)	C(2)-C(3)-C(4)	121.7(9)
C(5)-C(6)	1.414(10)	C(3)-C(4)-C(5)	119.3(9)
C(6)-C(7)	1.440(9)	C(4)-C(5)-C(6)	120.5(8)
C(7)-C(8)	1.437(10)	C(5)-C(6)-C(7)	119.4(7)
C(7)-N(1)	1.302(9)	C(6)-C(1)-C(2)	121.6(6)
N(1)-O(2)	1.402(9)	C(6)-C(7)-N(1)	121.8(6)
N(2)-O(2)	1.391(10)	C(6)-C(7)-C(8)	130.4(6)
C(8)-N(2)	1.314(9)	C(7)-N(1)-O(2)	106.2(6)
C(8)-C(9)	1.485(9)	C(7)-C(8)-N(2)	111.0(6)
C(9)-O(3)	1.313(9)	C(7)-C(8)-C(9)	129.5(6)
C(9)-O(4)	1.209(8)	N(1)-C(7)-C(8)	107.7(6)
O(3)-C(10)	1.458(10)	N(1)-O(2)-N(2)	111.2(6)
		O(2)-N(2)-C(8)	103.9(6)
		N(2)-C(8)-C(9)	119.3(6)
		C(8)-C(9)-O(3)	112.7(6)
		C(8)-C(9)-O(4)	122.4(6)
		C(9)-O(3)-C(10)	116.1(7)
		O(3)-C(9)-O(4)	124.8(6)

sulfate) extract gave **3a** (0.8 g yield) (Table II). The ether-methanol solution was extracted with water; the aqueous layer was made acid with 2*N* hydrochloric acid and extracted with ether. The organic phase was extracted with a 1*N* mixture of CH_3COONa, acidified with 2*N* hydrochloric acid and finally extracted with ether. Evaporation of the dried (sodium sulfate) extract gave **4** as a white solid (Table I). Likewise from 1,2-benzisoxazole-3-acetic acid ethyl ester (**1b**) (7), using ethanol as a reaction solvent, **3b** (Table II) and **4** were obtained.

Reaction of 4-(2'-Hydroxyphenyl)furazan-3-carboxylic Acid (**4**) With Diethylamine.

A solution of **4** (1 g) and an excess of diethylamine (1.5 ml) in ethanol (10 ml) was heated under reflux for 3 hours. Then it was concentrated to a viscous oil which was purified by column chromatography to the highly unstable compound **5** (mp 92-93°), which spontaneously decompose to give 2-hydroxybenzonitrile (**6**).

4*H*-Furazan[3,4-*c*][1]Benzopyran-4-one (**7**).

Method A

Compound **4** (2.0 g) was dissolved in hot acetic anhydride (4 ml). A solid precipitated by cooling (80% yield) that was crystallized from *n*-hexane; mp 159-160°; ir (chloroform): 1790 (CO), 1630 cm^{-1} (C=N); nmr (DMSO-d_6); δ 7.58 (m, 2H, aromatic), 7.82 (m, 1H, aromatic), 8.26 (m, 1H, aromatic); ms: m/e (relative intensity) 188 (M^+, 100), 134 (56), 106 (94), and 70 (89).

Anal. Calcd. for $C_9H_4N_2O_3$ (MW 188.14): C, 57.45; H, 2.14; N, 14.89. Found: C, 57.33; H, 2.21; N, 15.01.

Method B.

N,N'-Dicyclohexylcarbodiimide (1.0 g) was added to a THF solution (40 ml) of compound **4** (1.0 g). After a night at room temperature the precipitated *N,N'*-dicyclohexylurea was filtered off and the solvent evaporated to give **7** (85% yield).

4-(2'-Hydroxyphenyl)furazan-3-carboxylic Acid Methyl (**8**) and Ethyl Ester (**9**).

Method A.

Following standard procedure compounds **8** and **9** were obtained from **4** and the corresponding alcohol as low melting solids (Table I). By reacting with acetic anhydride they formed monoacetate derivatives **19** and **20** (Table I).

Method B.

Compounds **8** and **9** were also obtained in quantitative yield by heating **7** for few minutes with the corresponding alcohol and then working up the mixture as usual.

4-(2'-Hydroxyphenyl)furazan-3-carboxylic Acid Dimethylamide (**10**), Diethylamide (**11**) and Anilide (**12**).

A slight excess of an ether solution of the appropriate amine was added to an ether solution of **7**. After 24 hours at room temperature the solution was evaporated to give the corresponding derivatives (Table I).

Reaction of **4** With Diazomethane.

An ether solution of **4** was treated at 0° with an excess of ether solution of diazomethane. After a night at room temperature, the solvent was evaporated and the residue separated into two main fractions through column chromatography. The first fraction (R*f* 0.303) was 4-(2'-methoxyphenyl)furazan-3-carboxylic acid methyl ester (**21**) (70% yield) (Table I); the second fraction (R*f* 0.220) was the methyl ester **8**.

α-Bromo-1,2-Benzisoxazole-3-acetic Acid Ethyl Ester (**13b**).

It was obtained following the procedure described for the methyl ester (**13a**) (11). Its physicochemical properties are reported in Table II.

Reaction of α-Bromo-1,2-benzisoxazole-3-acetic Acid Methyl Ester (**13a**) With Sodium Nitrite.

A solution of sodium nitrite (1.7 g) in water (10 ml) was added to a solution of **13a** (1.5 g) in methanol (20 ml) and kept at room temperature for 6 days. The mixture was then evaporated and the residue washed thoroughly with ether. The ether solution gave an oil which was purified by column chromatography to give α-hydroxy-1,2-benzisoxazole-3-acetic acid methyl ester (**15a**) (Table II). The solid residue was dissolved in water, acidified and then extracted with ether to give an oil which was purified by column chromatography. The first fraction was identical to compound **3a** and was identified as *E*-α-(hydroxyimino)-1,2-benzisoxazole-3-acetic acid methyl ester; the second fraction was identified as the *Z*-isomer (**14a**).

Compound **3a** (or **14a**) dissolved in chloroform and added with a little hydrogen chloride gas isomerized in a few hours to a 3:2 mixture of **3a**

and **14a**.

Starting from the ethyl ester **13b** and following the same procedure compounds **15b**, **3b** and **14b** were obtained.

α-(Hydroxyimino)-1,2-benzisoxazole-3-acetic Acid (**16**).

Compounds **3** and **14** (1.0 g) were refluxed with 6*N* hydrochloric acid (40 ml) during 1 hour. Cooling the solution gave a white solid whose physicochemical properties are reported in Table II.

When dissolved in 2*N* sodium hydroxide **16** gave furazane **4** by acidification.

Compound **16**, treated with acetic anhydride on a steam bath gave the acetylderivative **17**, mp 65-67°, whose ir spectrum showed typical absorption at 1780 cm^{-1} (CO). It was quite unstable and easily decomposed to 1,2-benzisoxazole-3-carbonitrile (**18**) (13) by crystallization with water.

E- And *Z*-α-(Phenylcarbamoiloxyimino)-1,2-benzisoxazole-3-acetic Acid Ethyl Ester (**22** and **23**).

Compound **3b** (or **14b**) was dissolved in a slight excess of phenylisocyanate (0.75 mmole). Upon standing overnight at room temperature the mixture was treated with carbon tetrachloride and the white solid filtered and crystallized (Table II).

E-α-(Methoxyimino)-1,2-benzisoxazole-3-acetic Acid Ethyl Ester (**24**).

The ester **3b** treated with an excess of diazomethane as reported above gave **24** (Table II).

REFERENCES AND NOTES

(1) Presented at the 14th National Congress of the Italian Chemical Society, Catania, September 1981.

(2) M. Giannella, F. Gualtieri and C. Melchiorre, *Phytochemistry*, **10**, 539 (1971).

(3) M. Giannella, F. Gualtieri, C. Melchiorre and A. Orlandoni, *Chim. Thér.*, **7**, 127 (1972).

(4) M. Pigini, M. Giannella, F. Gualtieri, C. Melchiorre, P. Bolle and L. Angelucci, *ibid.*, **10**, 29 (1975).

(5) M. Pigini, M. Giannella, F. Gualtieri, C. Melchiorre, P. Bolle and L. Angelucci, *ibid.*, **10**, 33 (1975).

(6) Y. Masuda, T. Karasawa, Y. Shiraishi, M. Hori, K. Yoshida and M. Shimizu, *Arzneim.-Forsch.*, **30**, 477 (1980).

(7) G. Casini, F. Gualtieri and M. L. Stein, *J. Heterocyclic Chem.*, **6**, 279 (1969).

(8) A. J. Boulton, A. R. Katritzky and A. M. Hamid, *J. Chem. Soc. (C)*, 2005 (1967), and references cited therein.

(9a) R. A. Olofson and J. S. Michelman, *J. Org. Chem.*, **30**, 1854 (1965); (b) K. L. Stuart, *Heterocycles*, **3**, 651 (1975), and references cited therein.

(10) P. Pollet and S. Gelin, *Synthesis*, 977 (1979).

(11) H. Uno, M. Kurokawa, K. Natsuka, Y. Yamato and H. Nishimura, *Chem. Pharm. Bull.*, **24**, 632 (1976).

(12) H. Reinheckel, A. Jovtscheff and S. Spassov, *Monatsh. Chem.*, **96**, 1185 (1965).

(13) H. Nishimura, M. Shimizu, H. Uno, T. Hirooka, Y. Masuda and M. Kurokawa, *Japan Kokai*, 73 92,366, 30 Nov. 1973; *Chem. Abstr.*, **80**, 133416p (1974).

(14a) A. P. Stoll and F. Troxler, *Helv. Chim. Acta*, **51**, 1864 (1968); (b) P. Yates, E. S. Hand, *J. Am. Chem. Soc.*, **91**, 4749 (1969); (c) B. C. Tyson, E. J. Poziomek and E. R. Danielson, *J. Org. Chem.*, **34**, 3635 (1969), and references cited therein.

(15) P. Main, S. E. Hull, L. Lessinger, G. Germain, J. P. Declercq and M. M. Woolfson (1978). Multan 78. A system of computer Programmes for the Automatic Solution of Crystal Structures from X-ray Diffraction Data. Universities of York, England and Louvain, Belgium.

(16) S. Cerrini and R. Spagna, Abstract of the 4th European Crystallographic Meeting, Oxford, A, 7 (1977).