Studies on 2,1-Benzisoxazoles and Related Heterocycles. Reaction of Diazomethane with 6-Nitro-2,1-benzisoxazoles and Nitrobenzofurazan Oxides

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Some 7-methyl-substituted-2,1-benzisoxazoles and cyclopropanobenzofurazan oxides are synthesized and characterized by their elemental and spectral analyses.

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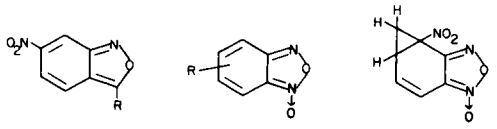
In 2,1-benzisoxazoles, chemical as well as physical methods of analysis have revealed exceptionally low electron density at C-3 and consequently the proton at this carbon is highly acidic (1). Deprotonation at C-3 is usually accomplished under base catalysed ring opening reaction of these compounds (2). Recently (3), 3-methyl-2,1-benzisoxazole and 1,3-dimethyl-2,1-benzisoxazole salts are shown to react with aromatic aldehydes and ketones giving highly coloured styryl derivatives. Carbon nucleophiles derived from active methylene compounds (4), hydride, cyanide and azide (5) ions are assumed to initiate the isoxazole ring opening by initial nucleophillic attack at C-3. We report here the reaction of diazomethane with 6-nitro-2,1-benzisoxazoles and nitrobenzofurazan oxides which had more than one potential site for reaction.



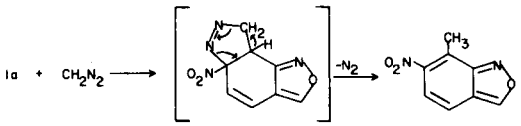
1 2 3

a, R = H
b, = COOH
c, = $COOCH_3$
d, = $COOCH_2CH_3$
e, = $COOCH(CH_3)_2$

a, R = H
b, = 4-NO_2
c, = 5-NO_2

Benzisoxazole **1a** and **1b** were prepared through pyrolysis of 2,4-dinitrophenylacetic acid, essentially employing the procedure of Eckroth and Cochran (6) with the modification of avoiding sublimation under vacuum, **1a** and **1b** were obtained in yields 20% and 50%, respectively; **1c-1e** were prepared by acid catalysed esterification of **1b**.

When **1a** was allowed to react with an excess of ethereal solution of diazomethane at room temperature for eight hours, removal of the solvent and residue thus obtained on recrystallisation from petroleum ether gave methylated benzisoxazole (**4a**). The characteristics of these benzisoxazoles are recorded in Table I. Interestingly, the C-3 proton remained intact and also there was no evidence for the formation of any other detectable product, showing that reaction with the nitro group (7) or at any other position in the isoxazole ring did not occur. The benzisoxazole **4a** did not react further when the reaction was conducted over longer periods.



X 4a

The pmr spectrum of **4** showed some interesting features. The pmr (60 MHz, deuteriochloroform) of benzisoxazole (**4a**) did not show AB doublets of the H_4 and H_5 protons but rather a broad singlet integrating for two protons. However, a single broad line at δ 7.50 could be resolved by recording the pmr at 300 MHz in deuteriochloroform the broad singlet being resolved into clear AB doublets at δ 7.56 (9.4 Hz) and δ 7.48 (9.4 Hz). The pmr spectral data of these benzisoxazoles is recorded in Table II. A general feature emerges from this data, *i.e.*, in 7-methylbenzisoxazoles (4), the H_3, H_4, H_5 protons were shifted significantly upfield.

When **1a** was allowed to react with ethereal diazomethane at 0°, the fast moving spot (tlc) for **4a** did not appear, rather, over several hour's time, there was a fixed spot which during workup appeared to be converted to the same fast moving spot as in the case of the reaction of diazomethane with **1a** at room temperature. We believe the methylation at C_7 goes through the initial unstable cycloadduct (X), whose formation is followed by collapse into the C_7-methyl. All attempts to isolate such a dipolar cycloadduct failed. The benzisoxazole without the 6-nitro group did not react with diazomethane. When benzofurazan oxides **2a** or **2c** [benzofurazan oxides **2a-c** were prepared by known procedures (8)] were allowed to react with diazomethane in a similar manner, the reaction was complete at room temperature in 24 hours. The usual workup did not give any stable characterisable product (9). However, 4-nitrobenzo-

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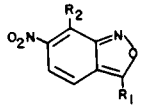
Table I

Physical and Analytical Data for Compounds **1** and **4**



Compound No.	R_1	R_2	Yield %	°C	Solvent of Crystallisation	Formula	Analyses Calculated C	H	N	Found C	H	N
1a	H	H	20	133.00	Ethanol	$C_7H_4N_2O_3$	51.22	2.44	17.07	51.05	2.28	17.30
1c	$COOCH_3$	H	80	152.00	Methanol	$C_9H_6N_2O_5$	48.64	2.70	12.61	48.30	2.91	12.65
1d	$COOC_2H_5$	H	75	116.50	Benzene	$C_{10}H_8N_2O_5$	50.85	3.35	11.86	50.62	3.28	12.10
1e	$COOCH(CH_3)_2$	H	75	134.50	Petroleum ether	$C_{11}H_{10}N_2O_5$	52.80	4.00	11.20	53.05	4.10	11.15
4a	H	CH_3	90	113.00	Petroleum ether	$C_8H_6N_2O_3$	53.93	3.37	15.73	53.68	3.22	15.92
4c	$COOCH_3$	CH_3	80	118.50	*n*-Pentane	$C_{10}H_8N_2O_5$	50.85	3.35	11.86	50.65	3.48	12.12
4b	$COOC_2H_5$	CH_3	75	70.00	*n*-Hexane	$C_{11}H_{10}N_2O_5$	52.80	4.00	11.20	52.72	4.08	11.28
4e	$COOCH(CH_3)_2$	CH_3	80	102.50	Petroleum ether	$C_{12}H_{12}N_2O_5$	54.55	4.55	10.61	54.48	4.65	10.75

Table II

^{1}H-NMR Data for Compounds **1** and **4**

Compound No.	Solvent	Chemical shift of H_3	H_4	H_5	H_7/CH_3	J_{H_4,H_5} in Hz	Other chemical shifts and coupling constants
1a	Deuteriochloroform	**9.37**	7.81	7.82	8.66	9.40	J_{H_3,H_7} = 1.1 Hz; J_{H_3,H_7} = 1.4 Hz; J_{H_4,H_7} = 1.1 Hz.
1c	Perdeuteriobenzene		7.30	7.42	8.06	10.00	OCH_3; 3.55 (s, 3H).
1d	Perdeuteriobenzene		7.00	6.77	7.53	10.00	OCH_2CH_3; 3.50 (q, 2H); 0.5 (t, 3H).
1e	Carbon tetrachloride		7.90	8.01	8.70	10.00	$OCH(CH_3)_2$; 5.40 (m, 1H); 1.51 (d, 6H).
4a	Deuteriochloroform	9.27	7.48	7.56	2.85	9.40	J_{CH_3, H_3} = 0.6 Hz.
4c	Perdeuteriobenzene		7.31	7.03	2.45	10.00	OCH_3; 3.38 (s, 3H).
4d	Carbon tetrachloride		7.87	7.57	2.88	10.00	OCH_2CH_3; 4.56 (q, 2H); 1.56 (t, 3H).
4e	Carbon tetrachloride		7.80	7.50	2.83	10.00	$OCH(CH_3)_2$; 5.27 (m, 1H); 1.47 (d, 6H)

furazan oxide gave a yellow crystalline solid m.p. 89-90° in 20% yield and is assigned structure **3** which is supported by elemental as well as spectral analysis. The isolation of **3** strongly suggests the initial formation of a 1,3-cycloadduct (X) followed by loss of nitrogen and therefore also extends support to the proposed mechanism in the benzisoxazole series.

EXPERIMENTAL

Melting points were taken in open capillaries in a Büchi apparatus and are uncorrected. The nmr spectra were recorded on a Varian T-60 and Varian 300 MHz instrument and chemical shifts values are recorded in δ, parts per million, relative to the internal standard (tetramethylsilane). Mass spectra were determined on a AEI MS 30 instrument.

6-Nitro-2,1-benzisoxazole (**1a**) and 6-Nitroanthroxanic Acid (**1b**).

2,4-Dinitrophenylacetic acid (22.5 g.) in concentrated sulphuric acid (165 ml.) was heated at 120-130° for 2 hours. The solution was cooled to room temperature and poured into crushed ice (500 g.) and the solution was extracted with ether (2 x 200 ml.). Removal of the solvent gave a residue which was treated with 8% aqueous sodium bicarbonate solution (200 ml.), filtered and washed with 4% sodium bicarbonate solution (30 ml.) and finally washed with water. The residue on recrystallisation from ethanol gave an off-white solid **1a** (20%) m.p. 133°. The combined mother liquor on acidification with concentrated hydrochloric acid gave a red solid which was crystallised from hot water to obtain straw coloured crystals of **1b** (50%) m.p. 177° (remelted at 290°).

Esterification of 6-Nitroanthroxanic Acid (**1b**).

Concentrated sulphuric acid (5 ml.) was added dropwise to a solution of 2.5 g. of **1b** in 75 ml. of absolute methanol cooled to 0°. The solution was refluxed for one half hour, poured into 100 ml. of ice-cold water, extracted with ether (3 x 100 ml.) and dried over sodium sulphate (anhydrous). Solvent was removed and the residue, on recrystallisation from methanol, gave 2.13 g. of **1c** (80%) m.p. 152°.

Reaction Between 6-Nitro-2,1-benzisoxazole (**1a**) and Diazomethane.

A solution of **1a** (1.0 g.) in dry ether (50 ml.) and 4 equivalents of diazomethane in dry ether (30 ml.) were allowed to react for eight hours at room temperature. The solvent was removed under reduced pressure and the residue thus obtained was recrystallised from petroleum ether, 0.96 g. (90%) m.p. 113°; nmr: (300 MHz, deuteriochloroform): δ 9.27 (s, 1H), δ 7.56 (d, 1H), δ 7.48 (d, 1H), δ 2.85 (s, 3H); ms: (10) 178 (26.6%) M^+, 161 (30%), 118 (10%), 105 (26%), 90 (13.6%), 77 (100%), 64 (26.5%), 52 (80%).

Anal. Calcd. for $C_8H_6N_2O_3$: C, 53.93; H, 3.37; N, 15.73. Found: C, 53.68; H, 3.22; N, 15.92.

Reaction of 4-Nitrobenzofurazan Oxide (**2b**) with Diazomethane.

A solution of **2b** (1.5 g.) in 250 ml. of dioxane-ether (1:1) was allowed to react with 4.5 equivalents of diazomethane in dry ether (50 ml.). Workup as above gave a pasty residue which was purified by preparative thin layer chromatography employing benzene as eluent, giving two components. The major compound (70%) was a pasty polymeric material and the minor component was **3** (20%) m.p. 89-90°; nmr (220 MHz, deuteriochloroform): δ 1.28 (m, 1H), δ 3.08 (m, 1H), δ 3.24 (m, 1H), δ 6.44 (d, 1H) and δ 6.34 (dd, 1H). ms: 195 (100%) M^+, 179 (41%), 178 (30.1%), 163 (22.1%), 149 (57.1%), 136 (42%), 135 (76.2%), 133 (98%), 118 (46.2%), 104 (52%), 87 (79%), 77 (60%).

Anal. Calcd. for $C_7H_5N_3O_4$: C, 43.08; H, 2.56; N, 21.54. Found: C, 43.15; H, 2.45; N, 21.70.

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(9) This has been observed independently by other workers also (Dr. A. J. Boulton private communication).

(10) All the benzisoxazoles recorded showed required M^+ ions in the mass spectrometer followed by loss of M^+-17 due to $-OH$ and (M^+-17)-28 due to $-CO$, diagonistic of *o*-nitrotoluenes.