Unexpected Behaviour of the Oxidizing Agent Sodium *m*-Nitrobenzenesulfonate: Synthesis of a New Class of 5-Hydroxy[1]benzopyrano-[4,3-*c*]pyridazin-3(2*H*)-ones

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Sodium *m*-nitrobenzene sulfonate, widely used in dehydrogenation of 4,5-dihydro-3(2*H*)-pyridazinones to their corresponding aromatic derivatives, behaves in an unexpected way when 4,4a-dihydro-5*H*[1]benzopyrano[4,3-*c*]pyridazin-3(2*H*)-ones are employed as substrate. The synthesis of a new class of 5–hydroxy[1]benzopyrano[4,3-*c*]pyridazin-3(2*H*)-ones is described.

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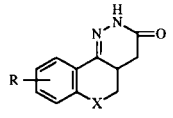
Aryl-4,5-dihydro-3(2*H*)-pyridazinones and their rigid tricyclic analogues together with the corresponding aromatic derivatives have been widely reported as antihypertensive, inotropic and platelet antiaggregating agents [1,2].

Aromatization of the dihydro derivatives is normally accomplished by bromine in glacial acetic acid [3]. However, in the case of compounds containing activating substituents on the phenyl ring, concomitant bromination of the aromatic moiety occurs [4]. An alternative pathway using *m*-nitrobenzenesulfonate has first been described by Bachmann [5] and since then it has largely been employed by many authors [6,7].

In the course of our studies on new cardiovascular agents we have also used this reagent on several tetrahydrobenzo[*h*]cinnolinones **1**, obtaining the desired dehydrogenation in good yield [8].



1, X = CH_2
2, X = O

a, R = 9–OCH_3, **b**, H, **c**, 8–OCH_3

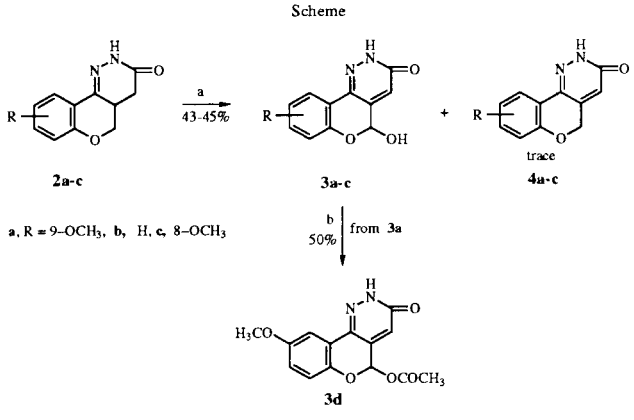
Figure 1

We report in this paper the unexpected results we obtained by employing the same method on the bioisoster structure of 4,4a-dihydro-5*H*-[1]benzopyrano[4,3-*c*]pyridazin-3(2*H*)-ones **2** in order to prepare the corresponding aromatic derivatives **4**, see Scheme. Quite surprisingly, in fact, when we reacted **2a** with equimolar *m*–nitrobenzenesulfonate in basic medium, the expected **4a** was present only in traces, the main product being **3a**, to which the structure of 5-hydroxy-9-methoxy[1]benzopyrano[4,3-*c*]pyridazin-3(2*H*)-one was assigned on the basis of analytical and spectral (^{1}H-nmr, ms) data and of its easy conversion with acetic anydride in pyridine to the acetyl derivative **3d**, see Scheme.

To verify the validity of this method, the same oxidation was then extended to the unsubstituted compound **2b** and to the 8-methoxy isomer **2c**. In both cases the corresponding 5-hydroxy derivatives **3b** and **3c** were obtained in good yields. These results open the way to the synthesis of a still unknown class of benzopyranopyridazinones functionalized at position 5 with a hydroxy group, which in turn could represent key intermediates for a variety of new 5-substituted derivatives.

It is to be noted that the initially desired compounds **4a–c** were obtained, though in low yields, by using chloranil in refluxing *p*-xylene [9].

Scheme



2a-c **3a-c** **4a-c**

a, R = 9–OCH_3, **b**, H, **c**, 8–OCH_3

a) Sodium *m*-nitrobenzenesulfonate/NaOH/Δ, b) $(CH_3CO)_2O$/pyridine.

Table I

Physical and Spectral Data of Compounds **3a-d**

Compound	Yield %	mp°C	IR cm^{-1}	Formula	1H-NMR δ (ppm)	Elemental analyses Calcd./Found C	H	N
3a	45	200-202	3300-3100 1600	$C_{12}H_{10}N_2O_4$ (246.2)	3.8 (s, 3H, OCH_3), 6.2 (d, 1H, H5), 6.8 (s, 1H, H4), 7.0 (app s, 2H arom), 7.4 (app s, 1H arom),7.9 (d, 1H, OH), 13.2 (s, 1H, NH)	58.54 58.78	4.09 3.98	11.38 11.07
3b	43	210-212	3300-3100 1600	$C_{11}H_8N_2O_3$ (216.2)	6.2 (d, 1H, H5), 6.8 (s, 1H, H4), 6.9-7.4 (m, 4H arom), 8.0 (d, 1H, OH), 13.1 (s, 1H, NH)	61.12 59.89	3.73 3.97	12.96 13.04
3c	45	198-200	3300-3100 1600	$C_{12}H_{10}N_2O_4$ (246.2)	3.8 (s, 3H, OCH_3), 6.2 (d, 1H, H5), 6.8 (s, 1H, H4), 6.9-7.6 (m, 3H arom), 8.0 (d, 1H, OH), 13.2 (s, 1H, NH)	58.54 58.21	4.09 4.15	11.38 10.99
3d	50	145-148	1740 1660	$C_{14}H_{12}N_2O_5$ (288.3)	2.0 (s, 3H, $COCH_3$), 3.8 (s, 3H, OCH_3), 7.0-7.4 (m, 5H, H5 + 4H arom), 13.6 (s, 1H, NH)	58.33 58.27	4.20 4.14	9.72 9.87

EXPERIMENTAL

Melting points were determined on a Büchi 510 capillary melting point apparatus and are uncorrected. The ir spectra were recorded on a Perkin-Elmer 1310 infrared spectrophotometer. The ^{1}H-nmr spectra were recorded on a Varian XL 200 spectrometer; chemical shifts are reported as δ (ppm), relative to tetramethylsilane as the internal standard; DMSO-d_6 was used as the solvent, unless otherwise noted. TLC on silica gel 60 (Merck; 70-230 mesh) was used for column chromatography. Analyses (hplc) were performed using a Zorba CN column (4.6 x 25 mm) with a flow rate of 1.0 ml/minute and detection at 230 nm (eluent water/acetonitrile 85/15, 0.2% triethylamine and phosphoric acid to *p*H 7.8). Mass spectra were obtained at 70 eV with a Varian 112 mass spectrometer, using a direct-inlet system.

5-Hydroxy[1]benzopyrano[4,3-*c*]pyridazin-3(2*H*)-ones **3a-c**.

General Method

A mixture of the required dihydrobenzopyranopyridazinone **2** [9] (0.006 mole), sodium *m*-nitrobenzene sulfonate (0.006 mole), sodium hydroxide (0.025 mole) and water (60 ml) was refluxed for 1 hour. After cooling, the resulting brown solution was acidified with 6 *N* hydrochloric acid, the thus-formed precipitate filtered and further purified by column chromatography, eluting with dichloromethane/methanol 95/5. Traces of pyridazinones **4** were collected as the first run, immediately followed by **3**, see Table I for data.

5-Acetoxy-9-methoxy[1]benzopyrano[4,3-*c*]pyridazin-3(2*H*)-one **3d**.

A solution of **3a** (0.5 g, 0.002 mole) and acetic anhydride (0.6 ml, 0.006 mole) in pyridine (3 ml) was stirred at room temperature overnight. After diluting with water, the mixture was acidified with 2 *N* hydrochloric acid. The thus-formed precipitate was filtered and triturated with ethanol to give 0.28 g (50%) of **3d**, see Table I for data.

REFERENCES AND NOTES

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