Synthesis of New Spirobenzazolines Including a Furo[3,4-*b*]pyran Ring System

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A series of 4,5-dihydrofuro[3,4-*b*]pyran-6-spiro-2'-benzazolines **3** were prepared by reaction of 4,4-dimethyl-2,6-dioxo-4,5-dihydrofuro[3,4-*b*]pyran **1** with *o*-phenylenediamine, *o*-aminophenol, *o*-aminothiophenol or their derivatives. Most of these compounds exhibited a significant analgesic activity.

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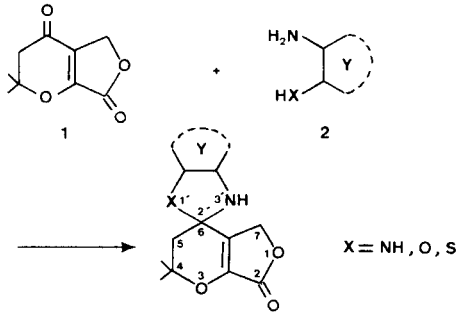
Spirobenzazolines are an interesting class of compounds owing to their pharmacological potentialities but only a few examples have been reported. Recently the treatment of a ketosugar derivative by some 1,4-binucleophiles led to the corresponding spiro compounds in good yields [1,2].

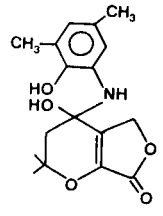
The purpose of this investigation is to develop a synthesis of several new spirobenzazolines including an original furo[3,4-*b*]pyran ring system which we formerly described [3]. In previous work we reported the reaction of arylamines with such a system affording the expected arylimines [4]. In the present paper we used arylamines ortho-substituted by an amino, hydroxy or thiol group.

The treatment of 4,4-dimethyl-2,6-dioxo-4,5-dihydrofuro[3,4-*b*]pyran **1** by an equimolecular amount of ortho-substituted arylamine **2** in boiling 2-propanol affords the spirobenzazolines **3** in good yields:



3

Spirobenzoxazolines (**3**, X = O) appeared less stable than spirobenzothiazolines and spirobenzimidazolines (**3**, X = S, NH). In one case, the spiro compound could not be obtained and the dihydroxyamino derivative **4** was isolated:



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Analogous observations were mentioned in the literature [5,6].

Moreover the formation of arylimines was not observed, as evidenced by thin layer chromatography and infrared spectrography.

The structure of compounds **3** was deduced from their analytical and spectral data (Tables 1 and 2). Unambiguous assignment of the spiro carbon 6 was supported by its own ^{13}C nmr chemical shift, near 103 ppm, by comparison with that of the corresponding carbon in arylimines, near 148 ppm [4]. Furthermore we noted that most signals appeared as multiplets on ^{13}C nmr spectra, suggesting the presence of isomers and probably a nitrogen inversion hindrance. By heating to 120° a solution of **3a** in DMSO-d_6, coalescence of these multiplets could be observed.

Spirobenzimidazolines **3a** to **3e** exhibited a significant analgesic activity in preventing painful abdominal crisis induced by phenylbenzoquinone peritoneal injection in mice [7]. Their potency was 30 to 60 per cent of the analgesic effect of acetylsalicylic acid used as reference. Spirobenzoxazolines **3f** to **3h** and spirobenzothiazoline **3i** were less potent whereas open ring compound **4** was inactive.

EXPERIMENTAL

All melting points were determined on a Kofler apparatus and were uncorrected. The infrared spectra were recorded on a Beckman 4240 spectrophotometer. The proton nmr spectra were recorded on a Varian EM 360 A in DMSO-d_6. Resonance positions are given on the δ scale (parts per million) relative to internal tetramethylsilane. The nmr peaks were designated as follows: s, singlet; d, doublet; m, multiplet. The ^{13}C nmr spectra were recorded on a Brucker AC 200 50 MHz spectrophotometer. Elemental analysis were performed at the Service Central d'analyse, Centre National de la Recherche Scientifique, 69390 Vernaison, France. The tlc were performed on silicagel G plates with ethyl acetate-hexane (6:4) and the plates were visualized with uv light and/or iodine vapor. Organic solutions were dried over anhydrous sodium sulfate.

4,4-Dimethyl-2,6-dioxo-4,5-dihydrofuro[3,4-*b*]pyran (**1**).

This compound was prepared as previously described [3].

4,4-Dimethyl-2-oxo-4,5-dihydrofuro[3,4-*b*]pyran-6-spiro-2'-benzazolines **3**.

Table 1

Physical and Analytical Data for Compounds **3**

Compound No.	X		Yield [a] %	Rf	mp °C	Molecular Formula	Analysis % Calcd./Found C	H	N	O	S
3a	NH	Phenyl	95	0.30	234	$C_{15}H_{16}N_2O_3$	66.18	5.88	10.29	17.65	
							66.25	5.96	10.62	17.17	
3b	NH	4-methylphenyl	61	0.43	250	$C_{16}H_{18}N_2O_3$	67.13	6.29	9.79	16.79	
							67.06	6.29	9.75	16.95	
3c	NH	4,5-dimethylphenyl	62	0.46	225	$C_{17}H_{20}N_2O_3$	68.00	6.67	9.33	16.00	
							67.90	6.78	9.11	16.52	
3d	NH	4-benzoylphenyl	33	0.24	252	$C_{22}H_{20}N_2O_4$	70.21	5.32	7.45	17.02	
							70.02	5.40	7.25	17.38	
3e	NH	1,2-naphtyl	71	0.54	290	$C_{19}H_{18}N_2O_3$	70.80	5.59	8.70	14.91	
							71.02	5.43	8.77	14.52	
3f	O	Phenyl	86	0.81	198	$C_{15}H_{15}NO_4$	65.94	5.49	5.13	23.44	
							66.07	5.40	5.12	23.68	
3g	O	4-methylphenyl	61	0.69	148	$C_{16}H_{17}NO_4$	66.90	5.90	4.88	22.30	
							66.76	5.97	4.82	22.39	
3h	O	2,3-naphtyl	94	0.79	225	$C_{19}H_{17}NO_4$	70.59	5.28	4.33	19.82	
							70.82	5.36	4.19	19.95	
3i	S	Phenyl	95	0.54	220	$C_{15}H_{15}NO_3S$	62.28	5.19	4.85	16.62	11.07
							62.16	5.37	4.72	16.70	10.91

[a] Crude products.

Table 2

Spectral Data for Compounds **3**

Compound No.	IR (Potassium bromide) cm^{-1} ν N-H	ν C=O	ν C=C	δ N-H	^1H NMR (DMSO-d_6) δ (ppm)
3a	3300	1770	1645	1560	1.3 (s, 6H, 2 CH_3), 2.5 (s, 2H, 5-CH_2), 3.2 (s, 1H, NH), 5.1 (s, 2H, 7-CH_2-O), 7.0 (m, 4H, C_6H_4)
3b	3300	1770	1630	1570	1.4 (s, 6H, 2 CH_3), 2.3 (s, 3H, CH_3 of Y), 2.6 (s, 2H, 5-CH_2), 3.2 (s, 1H, NH), 5.2 (s, 2H, 7-CH_2-O), 7.0 (m, 3H, C_6H_3)
3c	3350	1760	1640	1570	1.4 (s, 6H, 2 CH_3), 2.2 (s, 6H, 2 CH_3 of Y), 2.5 (s, 2H, 5-CH_2), 3.2 (s, 1H, NH), 5.1 (s, 2H, 7-CH_2-O), 6.9 (d, 2H, C_6H_2)
3d	3300	1770	1620	1560	1.3 (s, 6H, 2 CH_3), 2.5 (s, 2H, 5-CH_2), 3.3 (s, 1H, NH), 5.1 (s, 2H, 7-CH_2-O), 7.3 (m, 8H, C_6H_5-CO-C_6H_3)
3e	3350	1770	1630	1550	1.4 (s, 6H, 2 CH_3), 2.5 (s, 2H, 5-CH_2), 3.5 (s, 1H, NH), 5.2 (s, 2H, 7-CH_2-O), 7.7 (m, 6H, $C_{10}H_6$)
3f	3540	1780	1640	1580	1.5 (s, 6H, 2 CH_3), 2.5 (s, 2H, 5-CH_2), 3.2 (s, 1H, NH), 5.2 (s, 2H, 7-CH_2-O), 7.2 (s, 4H, C_6H_4)
3g	3300	1770	1610	1570	1.4 (s, 6H, 2 CH_3), 2.4 (s, 3H, CH_3 of Y), 2.6 (s, 2H, 5-CH_2), 3.3 (s, 1H, NH), 5.2 (s, 2H, 7-CH_2-O), 7.2 (m, 3H, C_6H_3)
3h	3400	1770	1640	1570	1.5 (s, 6H, 2 CH_3), 2.6 (s, 2H, 5-CH_2), 3.3 (s, 1H, NH), 5.2 (s, 2H, 7-CH_2-O), 7.7 (m, 6H, $C_{10}H_6$)
3j	3350	1780	1640	1560	1.5 (s, 6H, 2 CH_3), 2.5 (s, 2H, 5-CH_2), 3.2 (s, 1H, NH), 5.2 (s, 2H, 7-CH_2-O), 7.6 (m, 4H, C_6H_4)

General Procedure.

A mixture of 4,4-dimethyl-2,6-dioxo-4,5-dihydrofuro[3,4-*b*]pyran (**1**) (3.64 g, 0.02 mole) and a suitable amount (0.02 mole) of *o*-phenylenediamine, *o*-aminophenol, *o*-aminothiophenol or their derivatives in 100 ml of 2-propanol was refluxed for 8 hours. After cooling, the crude products may precipitate and be filtered; otherwise the solvent was evaporated under reduced pressure and the residual mixture extracted with ethyl ether. Crude products were recrystallized from acetonitrile (**3a**) or ethanol (**3b** to **3f**).

4,4-Dimethyl-6-hydroxy-6-(3',5'-dimethyl-2'-hydroxy)phenylamino-2-oxo-4,5-dihydrofuro[3,4-*b*]pyran (**4**).

A mixture of 4,4-dimethyl-2,6-dioxo-4,5-dihydrofuro[3,4-*b*]pyran (**1**) (3.64 g, 0.02 mole) and 2-amino-4,6-dimethylphenol (2.46 g, 0.02 mole) in 100 ml of 2-propanol was refluxed for 8 hours. Then the compound **4** was obtained by the above described method, yield 6.10 g (96%), mp, 124°, Rf (ethyl acetate-hexane 6:4), 0.70; ir: 3500 (NH), 3400 (OH), 3000-2800 (CH_3), 1760 (CO), 1640 (C=C), 1600, 1500 (arom) cm^{-1}; ^1H nmr (DMSO-d_6): 1.40 (s, 6H, 2 CH_3), 2.20 (d, 6H, 2 CH_3 arom), 2.60 (s, 2H, CH_2), 3.30 (s,

1H, NH), 5.20 (s, 2H, CH_2-O-CO), 6.80 (s, 1H, OH), 7.00 (m, 2H arom), 10.2 (s, 1H, ArOH).

Anal. Calcd. for $C_{17}H_{21}NO_5$: C, 63.95; H, 6.58; N, 4.39; O, 25.05. Found: C, 63.80; H, 6.75; N, 4.30; O, 24.86.

Pharmacological Assay.

Compounds **3a** to **3i** were administered by the oral route to mice in 5 percent hydroxymethylcellulose suspension. Each animal received a 100 mg/kg dose of the assayed compound. A lot of 12 animals was used for evaluating each compound.

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REFERENCES AND NOTES

[1] J. M. J. Tronchet and B. Gentile, *Helv. Chim. Acta*, **59**, 1380 (1976).

[2] J. M. J. Tronchet and B. Gentile, *Helv. Chim. Acta*, **63**, 1779 (1980).

[3] M. Payard, J. Paris, J. M. Couquelet and J. D. Couquelet, *Bull. Soc. Chim. France*, 299 (1979).

[4] P. Coudert, J. M. Couquelet, P. Tronche, P. Bastide and F. Porte, *Ann. Pharm. France*, **43**, 291 (1985).

[5] J. Rondon, R. Guglielmetti and J. Metzger, *Bull. Soc. Chim. France*, 2581 (1971).

[6] E. K. Fifer, W. M. Davis and R. F. Borne, *Eur. J. Med. Chem.*, **19**, 519 (1984).

[7] J. R. Boissier and R. Simon, *Thérapie*, **20** 895 (1965).