Synthesis and Structural Study of Cyclopentane, Indene and Fluorene Spiro-derivatives

E. Galvez, G. G. Trigo,* M. Martinez and N. Cabezas

Departamento de Química Orgánica y Farmaceutica, Facultad de Farmacia, Universidad Complutense,
Madrid-3, Spain

Received June 24, 1982

The synthesis of three pharmacologically interesting series of cyclopentane, indene-2 and fluorene-9-spiro-5'-oxazolidine-2',4'-dione is described. Based on the data from ^{1}H and ^{13}C nmr spectra, the main conformational features of the above mentioned compounds is established.

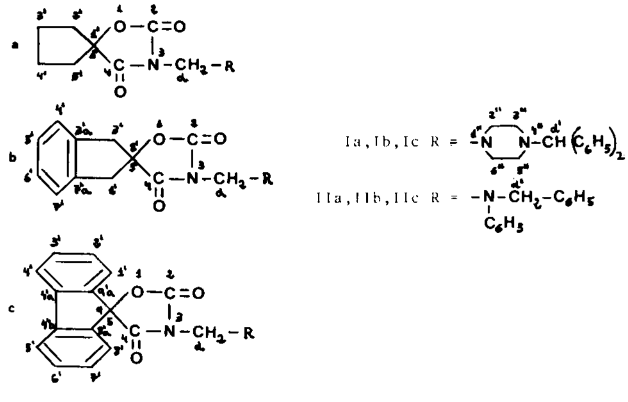
J. Heterocyclic Chem., **20**, 13 (1983).

Introduction.

In a previous paper (1) we reported the synthesis of cyclopentane, indane-2 and fluorene-9-spiro-5'-oxazolidine-2',4'-dione. In anticipation of a subsequent structure-activity relationship study we report here the synthesis and structural study by several methods of two series of 3'-(4-benzhydrilpiperazinomethyl) (Scheme I) and 3'-(*N*-benzyl-*N*-phenylaminomethyl) derivatives of the above mentioned compounds, keeping in mind the pharmacological properties of these substituents (2). The pharmacological study of the new compounds is now being carried out and anticholinergic properties have been found in compound Ic.

Scheme of the Synthesis.

In our previous paper (1) the synthesis of compounds X followed the sequence: III → IV → V → VII → VI → X (Scheme 1) (Except for compounds "c"). As the yields of the mentioned synthesis pathway were not good, we have carried out another synthesis procedure; the best ones found by us are Compounds "a": III → IV → V → IX → X; Compounds "b": III → IV → V → VIII → VII → IX → X; Compounds "c": VI → VII → IX → X.



Scheme 1

Treatment of compounds X with paraformaldehyde and a suitable amine yielded the corresponding 3'-derivatives Ia, Ib, Ic, and IIa, IIb, IIc.

IR Spectra.

As expected for compounds I in solid state, the piperazine ring adopts a chair conformation and the *N*-substituents are in an equatorial positions, consequently, the ir-spectra of compounds I, in the solid state, show two bands in the 2750-2800 cm^{-1} region (Bohlman's bands) due to the asymmetrical and symmetrical axial C-H stretching modes of the mechanical coupling when two C-H axial bonds are in a *trans*-coplanar position with respect to the lone pair of the nitrogen atom. These ir features are in accordance with those described by us in another piperazine derivative (3).

NMR Spectra.

The ^{1}H and ^{13}C nmr data are summarized in Table 1 and 2, in all cases noise decoupled and single frequency off resonance decoupling spectra were obtained.

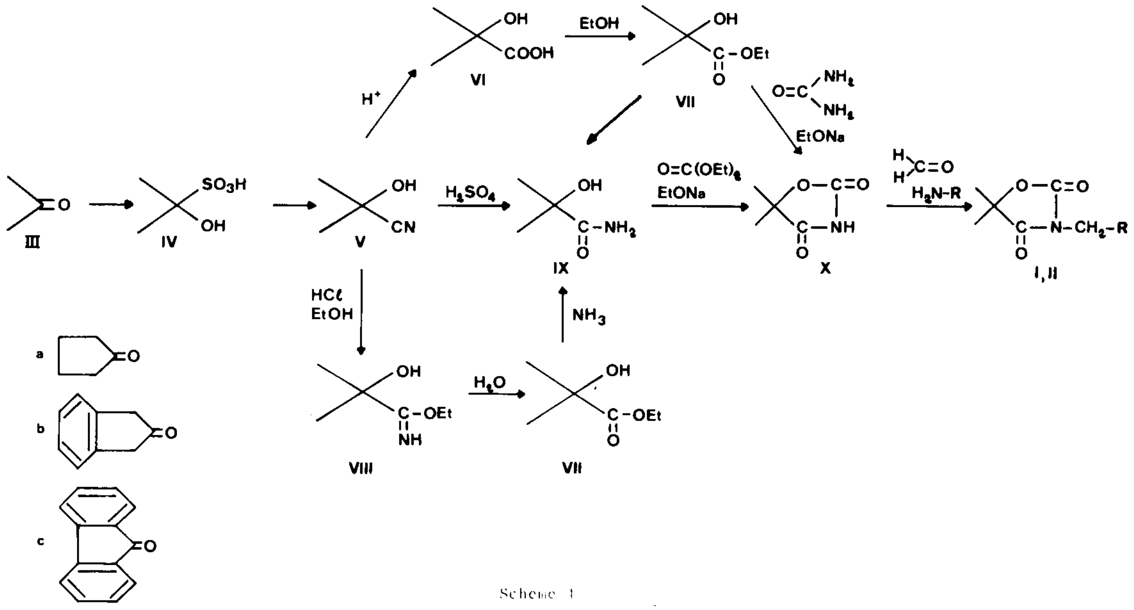
The singals of C-2'', C-3'', C-5'' and C-6'' are in agreement with a chair conformation of the piperazine ring since the shielding effect is not observed as a consequence of eclipsing between the C-2'' and C-3'' and the C-5'' and C-6'' hydrogen atoms in the boat conformer. The symmetry of the well-separated multiplets corresponding to H axial (δ = 2.3-2.5) and H equatorial (δ = 2.5-2.7) of the piperazine ring confirms the chair conformation deduced from ^{13}C nmr data.

The δ values of the piperazine carbon atoms clearly indicate the equatorial position of the radicals attached to the piperazine nitrogen atoms since for a *N*-axial position, a great interaction would be apparent at the piperazine protons and the axial *N*-groups, giving place to a shielding of $\sim$20 ppm for the piperazine carbon atoms (4).

By comparing the C-4 signal of Ic with the same carbon signals of Ia and Ib, a π-shielding effect of $\sim$4 ppm can be deduced from fluorene π-system.

EXPERIMENTAL

All melting points were taken in open capillary tubes and are uncorrected. Infrared spectra were determined using a Perkin-Elmer 577 spectrophotometer. The ^{1}H nmr spectra have been recorded using a Varian EM 390 operating at 90 MHz. The ^{13}C nmr spectra were determined on



Scheme 1

Table I

Chemical Shifts of Compounds I-II (a) in Deuteriochloroform (δ, Values; J, Hz Values; TMS as the Internal Reference)

Compound	1'(3')H	α-H	α'-H	Ar	CH-Ar	N-Ar
Ia (b)		4.5 s	4.2 s		7.0-7.7 m	
Ib	3.3 d, ^2J = 18, 3.6 d	4.5 s	4.2 s	7.1-7.4 m	7.1-7.4 m	
Ic		4.7 s	4.2 s	7.1-7.8 m	7.1-7.8 m	
IIa (c)		5.2 s	4.8 s		7.2 s	6.7-7.2 m
IIb	2.9 d, ^2J = 16, 3.3 d	5.1 s	4.7 s	6.7-7.3 m	6.7-7.3 m	6.7-7.3 m
IIc		5.2 s	4.7 s	6.6-7.6 m	6.6-7.6 m	6.6-7.6 m

(a) The abbreviations, d (doublet), m (multiplet), and s (singlet) are used. (b,c) Cyclopentane protons give rise to a multiplet at 1.75-2.2 and 1.7-1.9, respectively.

Table II

Carbon-13 Chemical Shifts of Compounds I-II in Deuteriochloroform (δ, Values; TMS as the Internal Reference)

Compound	C-2	C-4	C-5	C-α	C-2'',6''	C-3'',5''	C-α'	CH-Ar			
								C-ipso	C-o,o'	C-m,m'	C-p
Ia (a)	155.77	177.24	92.51	61.85	50.50*	51.61*	75.99	142.50	128.41**	127.80**	126.92
Ib (b)	155.70	176.20	91.63	62.33	50.74*	51.77*	76.19	142.58	128.61**	127.98**	127.07
Ic (c)	156.37	172.73	90.47	62.62	50.72*	51.38*	75.55	142.39	128.46**	127.80**	126.98

(a) C-2',5': 37.02; C-3',4': 25.07. (b) C-1',3': 43.53; C-3'a,7'a: 138.21; C-4',7': 127.81; C-5',6': 124.57. (c) C-1',8': 131.32*; C-2',7': 129.12*; C-3',6': 120.97; C-4',5': 123.78; C-4'a,4'b: 141.51; C-8'a,9'a: 138.98. (d) *,** Values may be interchanged.

Bruker WP 80 SY spectrometer operating at 20 MHz. Noise decoupled and single frequency off resonance decoupled spectra have been obtained. The mass spectra were determined on a Hitachi Perkin-Elmer RMU-6M spectrometer. The elemental analysis were made in a Carlo Erba Elemental Analyzer model 1104 equipped with a C.S.I. digital integrator model C SI 38.

Cyclopentanone (IIIa).

This compound was obtained from Aldrich Chemical Company.

2-Indanone (IIIb).

This compound was obtained as previously described (5).

Preparation of Compounds IVa and IVb.

To a solution of sodium bisulfite (0.2 mole) in water (52 ml) was added with stirring compound IVa or IVb (0.2 mole). The precipitated solid was filtered under reduced pressure, yield, IVa, 74%; IVb, 98%.

α-Hydroxycyclopentanecarbonitrile (Va).

To 0.882 mole of IVa in water (30 ml) was added dropwise a solution of potassium cyanide (0.882 mole) dissolved in water (118 ml). The mixture was stirred for 1 hour. The oily layer was separated. The aqueous layer was treated with two portions of diethyl ether (225 ml). The oily and ethereal layers were mixed and the ether was removed by evaporation under reduced pressure. An oil was obtained in a yield of 77%; ir (film): 3100-3600 (O-H), 2222 ($C\equiv N$) cm^{-1}.

2-Hydroxyindane-2-carbonitrile (Vb).

To 0.1 mole of IVb moisted with water until pasty consistence was added potassium cyanide (0.1 mole) dissolved in water (20 ml). To this mixture was added sodium bisulfite until $pH = 6$-6.5, then the mixture was stirred for 24 hours. The solid precipitated was filtered under reduced pressure, yield 85%; ir (potassium bromide): 3400 (O-H), 2240 ($C\equiv N$) cm^{-1}.

α-Hydroxycyclopentanecarboxamide (IXa).

Compound Va (0.68 mole) was added slowly to 98% sulfuric acid (76 ml) cooled at 0°. The mixture was maintained at room temperature for 24 hours. The resulting solution was added to powdered ice (228 g), filtered and neutralized with barium hydroxyde until $pH = 6$. The resulting mixture was filtered and concentrated under reduced pressure, and the precipitated solid recrystallized from ethanol, mp 130°; ir (potassium bromide): 3600-3100 (O-H, NH_2), 1685 (C=O), 1650 (NH_2) cm^{-1}.

Anal. Calcd. for $C_6H_{11}NO_2$: C, 55.79; H, 8.58; N, 10.84. Found: C, 55.97; H, 8.63; N, 11.05.

Ethyl 2-Hydroxycyclopentane-2-iminecarboxylate (VIIIb).

Anhydrous hydrogen chloride was bubbled into a solution of Vb (0.044 mole) in ethanol (160 ml) for 45 minutes with external cooling and magnetic stirring. The mixture was maintained at -10° for 96 hours. The precipitated solid was filtered off, suspended in water at 0°, neutralized with sodium bicarbonate and treated with three portions of diethyl ether (25 ml). The ethereal solution was dried with anhydrous sodium sulfate, filtered and concentrated under reduced pressure and the crystals were removed by filtration, yield 66%; ir (potassium bromide): 3300 (N-H), 1650 (C=N) cm^{-1}.

Anal. Calcd. for $C_{12}H_{15}NO_2$: C, 70.22; H, 7.36; N, 6.82. Found: C, 70.16; H, 7.20; N, 6.55.

Ethyl 2-Hydroxyindane-2-carboxylate (VIIb).

To a mixture of aqueous hydrochloric acid (10%, 20 ml), and diethyl ether (20 ml) was added VIIIb (0.024 mole). The resulting mixture was stirred for 30 minutes. The ethereal layer was separated. The aqueous layer was treated with three portions of diethyl ether. The ethereal layers were joined, concentrated under reduced pressure and the crystals were removed by filtration, mp 90° (92%); ir (potassium bromide): 3460 (O-H), 1720 (C=O) cm^{-1}.

Anal. Calcd. for $C_{12}H_{14}O_3$: C, 69.88; H, 6.84. Found: C, 69.57; H, 6.66.

9-Hydroxyfluorene-9-carboxylic Acid (VIc).

This compound was obtained from Aldrich Chemical Company.

Ethyl 9-Hydroxyfluorene-9-carboxylate (VIIc).

A solution of VIc (0.1 mole), 98% sulfuric acid (2 ml) in ethanol (225 ml) was refluxed for 6 hours, then the solution was concentrated *in vacuo*. The residue was treated with cold water (50 ml), neutralized with sodium carbonate and treated with three portions of diethyl ether (200 ml). The ethereal layers were joined, dried with anhydrous sodium sulfate, filtered and the solvent evaporated. The white precipitate was recrystallized from ethanol, mp 90° (88%); ir (potassium bromide): 3490 and 3370 (O-H), 1730 (C=O) cm^{-1}.

Anal. Calcd. for $C_{16}H_{14}O_3$: C, 75.57; H, 5.54. Found: C, 75.22; H, 5.39.

Preparation of Compounds IXb and IXc.

Anhydrous ammonia was bubbled into a solution of VII (0.1 mole) in ethanol (150 ml) until saturation. The mixture was maintained at 0° for 4 days and the crystals were removed by filtration.

2-Hydroxyindene-2-carboxamide (IXb).

This compound was obtained in a yield of 81%, mp 195°; ir (potassium bromide): 3600-3100 (O-H, NH_2), 1685 (C=O), 1650 (NH_2) cm^{-1}.

Anal. Calcd. for $C_{10}H_{11}NO_2$: C, 67.78; H, 6.78; N, 7.90. Found: C, 67.45; H, 6.80; N, 7.53.

9-Hydroxyfluorene-9-carboxamide (IXc).

This compound was obtained in a yield of 79%, mp 170°; ir (potassium bromide): 3445 (O-H), 3380, 3310 and 3275 (NH_2), 1670 (C=O), 1590 (NH_2) cm^{-1}.

Anal. Calcd. for $C_{14}H_{11}NO_2$: C, 74.66; H, 4.88; N, 6.22. Found: C, 75.01; H, 4.82; N, 5.94.

Preparation of Compounds Xa, Xb and Xc.

To a solution of sodium methoxide (sodium, 6.04 g in methanol, 105 ml) was added another solution of IX (0.263 mole) and diethyl carbonate (0.236 mole) in methanol (105 ml). The resulting mixture was refluxed for 24 hours, then the solution was concentrated *in vacuo* to dryness. The residue was dissolved in cold water (100 ml) and treated with diethyl ether (50 ml). The aqueous layer was neutralized with aqueous hydrochloric acid (5*N*) to $pH = 5$. The resulting solution was maintained at 0° and the solid precipitate was recrystallized from ethanol.

Cyclopentanespiro-5′-oxazolidine-2′,4′-dione (Xa).

This compound was obtained in a yield of 66%, mp 120°; ir (potassium bromide): 3220 (N-H), 1818 and 1755 (C=O) cm^{-1}. The mass spectrum of the product had a molecular ion-peak at m/e 155 with abundant fragment peaks at 114, 84, 70, 56, 55 and 41.

Anal. Calcd. for $C_7H_9NO_3$: C, 53.84; H, 6.40; N, 8.97. Found: C, 53.61; H, 5.87; N, 8.94.

Indene-2-spiro-5′-oxazolidine-2′,4′-dione (Xb).

This compound was obtained in a yield of 74%, mp 206-207° ir (potassium bromide): 3200 (N-H), 1810 and 1750 (C=O) cm^{-1}.

Anal. Calcd. for $C_{11}H_9NO_3$: C, 64.70; H, 4.90; N, 6.86. Found: C, 64.60; H, 4.64; N, 6.53.

Fluorene-9-spiro-5′-oxazolidine-2′,4′-dione (Xc).

This compound was obtained in a yield of 95%, mp 235-237°; ir (potassium bromide): 3200 (N-H), 1810 and 1750 (C=O) cm^{-1}. The mass spectrum of the product had a molecular ion-peak at m/e 252 with abundant fragment peaks at m/e 251, 181, 180, 165, 164, 163, 152, 151, 82, 75, 71, 69, 57, 55, 44 and 43.

Anal. Calcd. for $C_{15}H_9NO_3$: C, 71.70; H, 3.58; N, 5.57. Found: C, 71.71; H, 3.46; N, 5.41.

Preparation of Compounds Ia, Ib and Ic, and IIa, IIb and IIc.

A solution of X (0.01 mole) 40% aqueous formaldehyde (1 ml) and a suitable amine (0.01 mole) in ethanol (40 ml) was refluxed with magnetic stirring for 10 hours. The resulting solution was maintained at 0° for 24 hours and the solid precipitate was recrystallized from ethanol.

3′-[(4-Benzhydrylpiperazino)methyl]cyclopentanespiro-5′-oxazolidine-2′,4′-dione (Ia).

This compound was obtained in a yield of 81%, mp 215-215°; ir (potassium bromide): 2780 and 2800 (C-H ax), 1810 and 1735 (C=O) cm^{-1}. The mass spectrum of the product has a molecular ion-peak at m/e 419 with abundant fragment peaks at m/e 264, 252, 251, 167, 166, 165, 115, 114, 113, 97, 91, 56, 55, 42 and 41.

Anal. Calcd. for $C_{25}H_{29}N_3O_3$: C, 71.57; H, 6.96; N, 10.01. Found: C, 71.88; H, 6.82; N, 9.74.

3'-[(4-Benzhydrylpiperazino)methyl]indane-2-spiro-5'-oxazolidine-2',4'-dione (Ib).

This compound was obtained in a yield of 65%, mp 190°; ir (potassium bromide): 2800 and 2755 (C-H ax), 1810 and 1745 (C=O) cm^{-1}. The mass spectrum of the product had a molecular ion-peak at m/e 390, with abundant fragment peaks at m/e 300, 251, 216, 222, 167, 115, 91, 71, 70, 57, 56, 44 and 43.

Anal. Calcd. for $C_{29}H_{29}N_3O_3$: C, 74.49; H, 6.25; N, 8.98. Found: C, 74.80; H, 6.55; N, 8.72.

3'-[(4-Benzhydrylpiperazino)methyl]fluorene-9-spiro-5'-oxazolidine-2',4'-dione (Ic).

This compound was obtained in a yield of 76%, mp 170-171°; ir (potassium bromide): 2810 and 2760 (C-H ax), 1820 and 1750 (C=O) cm^{-1}. The mass spectrum of the product had abundant fragment peaks at m/e 252, 251, 168, 167, 165, 152, 91, 85, 56 and 44.

Anal. Calcd. for $C_{33}H_{31}N_3O_3$: C, 76.87; H, 5.66; N, 8.15. Found: C, 76.54; H, 5.48; N, 7.99.

3'-(*N*-Benzyl-*N*-phenylaminomethyl)cyclopentanespiro-5'-oxazolidine-2',4'-dione (IIa).

This compound was obtained in a yield of 80%, mp 91-92°; ir (potassium bromide): 1810 and 1735 (C=O) cm^{-1}. The mass spectrum of the product had a molecular ion-peak at m/e 350 with abundant fragment peaks at m/e 196, 195, 194, 183, 182, 114, 105, 104, 92, 91, 77, 67, 65, 56, 51 and 41.

Anal. Calcd. for $C_{21}H_{22}N_2O_3$: C, 71.97; H, 6.32; N, 7.99. Found: C, 72.30; H, 6.44; N, 7.68.

3'-(*N*-Benzyl-*N*-phenylaminomethyl)indane-3-spiro-5'-oxazolidine-2',4'-dione (IIb).

This compound was obtained in a yield of 94%, mp 70°; ir (potassium bromide): 1815 and 1735 (C=O) cm^{-1}. The mass spectrum of the product had a molecular ion-peak at m/e 398 with abundant fragment peaks at m/e 203, 196, 195, 194, 183, 182, 159, 147, 116, 115, 105, 104, 92, 91, 77, 65, 56, 51 and 40.

Anal. Calcd. for $C_{25}H_{22}N_2O_3$: C, 75.36; H, 5.56; N, 7.02. Found: C, 75.56; H, 5.37; N, 6.81.

3'-(*N*-Benzyl-*N*-phenylaminomethyl)fluorene-9-spiro-5'-oxazolidine-2',4'-dione (IIc).

This compound was obtained in a yield of 61%, mp 129-130°; ir (potassium bromide): 1810 and 1750 (C=O) cm^{-1}. The mass spectrum or the product and a molecular ion-peak at m/e 446 with abundant fragment-peaks at m/e 251, 197, 196, 194, 182, 180, 164, 163, 105, 104, 92, 91, 77, 65 and 51.

Anal. Calcd. for $C_{33}H_{31}N_2O_3$: C, 78.01; H, 4.96; N, 6.27. Found: C, 77.98; H, 5.24; N, 6.19.

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