SYNTHESIS OF SOME ISOMERIC *4H,10H*[1]BENZOXEPINO[4,3-*d*]ISOXAZOL-4-ONES AND *4H,10H*[1]BENZOXEPINO[3,4-*c*]ISOXAZOL-4-ONES AND BENZOTHIEPINO ANALOGS

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Abstract — The regiospecific formation of 5- or 3-(phenoxymethyl) or 5- or 3-(phenylthiomethyl)isoxazole-4-carboxylic acids is described. These isoxazoles are utilized as the starting material for the synthesis of isomeric *4H,10H*[1]benzoxepino-[4,3-*d*] or [3,4-*c*]isoxazol-4-one derivatives and benzothiepino analogs.

Heterobenzoxepin and heterobenzothiepin analogs of 6,11-dihydro-11-oxodibenz[*b,e*]oxepin or thiepin constitue a group of compounds of interest due to their pharmaceutical activities or as intermediaries in the synthesis of biologically active compounds[1-15]. Our aim was to explore synthetic routes to tricyclic systems containing an isoxazole moiety. The literature concerned with *4H,10H*[1] benzoxepino or benzothiepinoisoxazolone is limited to a single compound : *4H,10H*[1]benzoxepino-[4,3-*d*]isoxazol-4-one which was prepared by reaction of hydroxylamine with 5-hydroxy-3-oxo-2,3-dihydro[1]benzoxepin-4-carboxaldehyde[6]. We report here a facile entry to new isomeric *4H,10H*[1] benzoxepino or benzothiepinoisoxazol-4-ones with a [4,3-*d*] or [3,4-*c*] junction involving the construction of the benzoxepino or benzothiepino skeleton from appropriately functionalized isoxazole-4-carboxylic acids.

Isomeric pairs of *4H,10H*[1]benzoxepino or benzothiepino[4,3-*d*]isoxazol-4-ones (4a-c) or (5a) and *4H,10H*[1]benzoxepino or benzothiepino[3,4-*c*]isoxazol-4-ones (15a-c) or (16a) were unambiguously synthesized by cyclization of the isoxazole-4-carboxylic acids bearing a phenoxymethyl or a phenylthiomethyl group in the 5 or 3 position : (2a-c) and (3a) or (13a-c) and (14a) respectively. The preparation of the acids (2a-c) and (3a) involve the utilization of ethyl 5-hydroxymethylisoxazole-4-carboxylates (1a-c), the regioselective synthesis of which we have reported[16]. Reaction of compounds (1) with thionyl chloride afforded the chloromethyl derivatives which upon treatment with sodium phenoxide or sodium thiophenoxide and subsequent alkaline hydrolysis led to the acids

(2a-c) or (3a). The regiospecific access to the acids (13a-c) and (14a) was achieved starting from ethyl 3-oxo-4-phenoxybutanoate (7) or ethyl 3-oxo-4-(phenylthio)butanoate (8) by a sequence similar to that described for the synthesis of 3,5-disubstituted isoxazole-4-carboxylic acids from β-keto esters[17,18]. Spectral data of the intermediate 4-acylisoxazol-5(*4H*)-ones (11a-c) and (12a) are summarized in the Table 1.

Oxidation of the benzothiepinoisoxazolones (5a) and (16a) by means of *m*-chloroperbenzoic acid easily afforded the 1,1-dioxide derivatives (6a) and (17a).

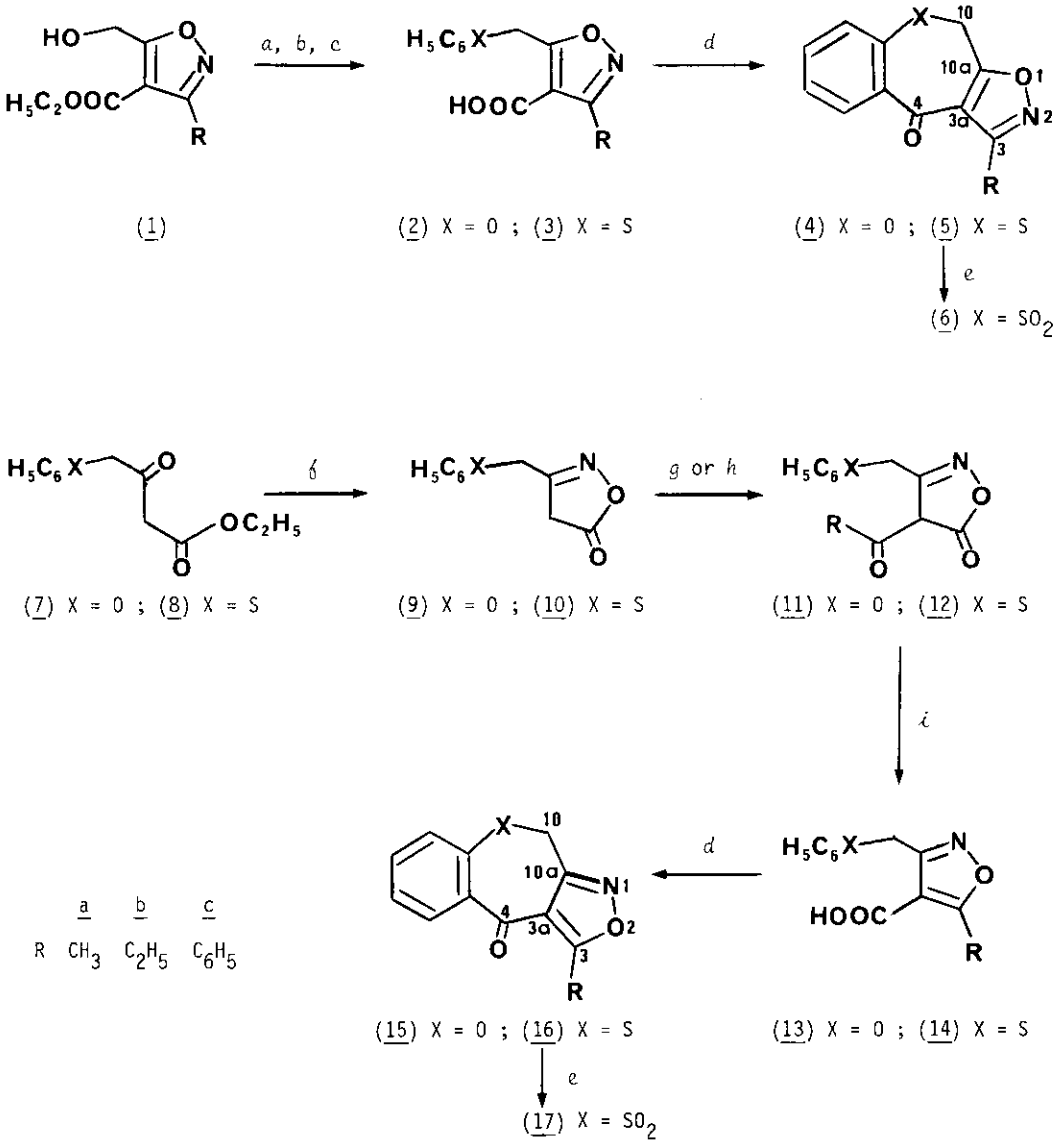
The structure of the tricyclic compounds was confirmed by the microanalyses and spectral data (Table 2). In the ^{13}C-NMR spectra of isomeric pairs of the benzoxepinoisoxazolones (4a) and (15a) or benzothiepinoisoxazolones (5a) and (16a) (Table 3), the carbon adjacent to the nitrogen resonates upfield as compared with the carbon adjacent to the isoxazole oxygen. These findings are consistent with the reported data for isomeric isoxazoles[16,19-22].

Table 1. Physical constants and spectral data of compounds (11) and (12)[a]

Compound	Yield[b] %	mp (°C)	Molecular formula[c]	IR ($CHCl_3$) (cm^{-1})	^{1}H-NMR (DMSO-d_6) δ (ppm), J (Hz)
(11a)	81	180	$C_{12}H_{11}NO_4$	3200-2500 1720	2.44 (s,3H); 5.15 (s,2H); 6.8-7.5 (m,5H); 10.1 (s,1H exchangeable with D_2O).
(11b)	68	201	$C_{13}H_{13}NO_4$	3200-2500 1715	1.05 (t,3H, J=7); 2.78 (q,2H, J=7); 5.20 (s,2H); 6.8-7.5 (m,5H); 9.3 (s, 1H exchang.).
(11c)	42	145	$C_{17}H_{13}NO_4$	3200-2500 1705	5.33 (s,2H); 6.9-7.9 (m,10H); 13.1 (s,1H exchang.).
(12a)	77	125	$C_{12}H_{11}NO_3S$	3200-2500 1715	2.60 (s,3H); 4.24 (s,2H); 7.2-7.6 (m,5H); 11.1 (s,1H exchang.).

[a] Compounds (11) and (12) exist as enolic form in analogy with previous findings concerning 4-acylisoxazol-5(*4H*)-one derivatives[23]. [b] Based on compounds (9) or (10). [c] The microanalyses were in satisfactory agreement with the calculated values (C, ± 0.28 ; H, ± 0.16 ; N, ± 0.24 ; S, ± 0.19).

Scheme



a, $SOCl_2$; *b*, $C_6H_5X^-$; c, 2N aqueous potassium hydroxide ; *d*, polyphosphoric acid ; *e*, *m*-chloroperbenzoic acid ; *f*, $NH_2OH.HCl$; *g*, triethyl orthoacetate and then 3% aqueous potassium hydroxide ; *h*, $(RCO)_2O$ / RCOONa ; *i*, 40% aqueous sodium hydroxide.

Table 2. Physical constants and spectral data of compounds (4), (5), (6), (15), (16) and (17)

Compound	Yield[a] %	mp (°C)	Molecular formula	IR ($CHCl_3$) (cm^{-1})	^{1}H-NMR ($CDCl_3$) δ (ppm), J (Hz)
(4a)	68[b]	116	$C_{12}H_9NO_3$	1655	2.60 (s,3H); 5.28 (s,2H);7.13-7.58 (m,3H); 8.07 (2d,1H,Jortho=8, Jmeta=2).
(4b)	68[b]	60	$C_{13}H_{11}NO_3$	1650	1.35 (t,3H,J=7); 3.08 (q,2H,J=7); 5.25 (s,2H); 7.13-7.68 (m,3H); 8.08 (2d,1H,Jortho=8, Jmeta=2).
(4c)	72[b]	177	$C_{17}H_{11}NO_3$	1655	5.37 (s,2H); 7.15-7.87 (m,8H); 8.10 (2d,1H, Jortho=8,Jmeta=2).
(5a)	63[b]	119	$C_{12}H_9NO_2S$	1645	2.58 (s,3H); 4.08 (s,2H); 7.40-7.75 (m,3H); 7.85-8.00 (m,1H).
(6a)	95[c]	189	$C_{12}H_9NO_4S$	1670, 1345, 1165	2.58 (s,3H); 4.82 (s,2H); 7.73-8.29 (m,4H).
(15a)	62[d]	180	$C_{12}H_9NO_3$	1655	2.83 (s,3H); 5.22 (s,2H); 7.08-7.58 (m,3H); 8.16 (2d,1H,Jortho=8, Jmeta=2).
(15b)	66[d]	201	$C_{13}H_{11}NO_3$	1650	1.39 (t,3H,J=7); 3.29 (q,2H,J=7); 5.21 (s,2H); 7.13-7.73 (m,3H); 8.18 (2d,1H,Jortho=8, Jmeta=2).
(15c)	49[d]	145	$C_{17}H_{11}NO_3$	1650	5.28 (s,2H); 7.18-7.85 (m,6H); 7.98-8.35 (m,3H).
(16a)	44[d]	125	$C_{12}H_9NO_2S$	1650	2.82 (s,3H); 4.02 (s,2H); 7.40-7.72 (m,3H); 7.95-8.10 (m,1H).
(17a)	95[e]	197	$C_{12}H_9NO_4S$	1670, 1345, 1170	2.84 (s,3H); 4.73 (s,2H); 7.68-8.29 (m,4H).

[a] Yield of isolated pure materials based on : [b] compound (1), [c] compound (5a), [d] compounds (11) or (12), [e] compound (16a). The microanalyses were in satisfactory agreement with the calculated values (C, ± 0.27 ; H, ± 0.30 ; N, ± 0.15 ; S, ± 0.29).

Table 3 - Pertinent ^{13}C-NMR spectral data of compounds (4a, 15a) and (5a, 16a) (hexadeuterioacetone) δ (ppm), J (Hz)

Compound	C-3	C-3a	C-4	C-10	C-10a
(4a)	160.8 (q, ^{2}J=7)	118.2	181.2	66.9	175.5 (t, ^{2}J=5)
(15a)	178.2 (q, ^{2}J=7)	116.6	181.4	66.9	160.8 (t, ^{2}J=4)
(5a)	161.6 (q, ^{2}J=5.5)	117.8	185.6	29.6	177.2 (t, ^{2}J=6)
(16a)	179.2 (q, ^{2}J=7)	117.1	185.7	30.1	162.4 (t, ^{2}J=6)

EXPERIMENTAL

All melting points were determined on a Kofler block. Infrared spectra were obtained with a Beckman Model Acculab 2 spectrometer. ^{1}H-NMR spectra were recorded on a Brucker WP 80 spectrometer. ^{13}C-NMR spectra were performed on a Varian XL-100 12FT. All spectra are recorded in δ units downfield from Me_4Si. Elemental analyses were determined by Microanalytical Laboratory, Centre National de la Recherche Scientifique, 69390 Vernaison France.

Compounds (1a-c)[16] *and* (9)[24] *were prepared as previously described.*

4H,10H[1]Benzoxepino[4,3-*d*]isoxazol-4-ones (4a-c) and *4H,10H*[1]Benzothiepino[4,3-*d*]isoxazol-4-one (5a)

To a solution of compound (1)[16] (30 mmol) in chloroform (20 ml) was added dropwise a solution of thionyl chloride (7.1 g, 60 mmol) in chloroform (10 ml). The mixture was refluxed for 2 h and the solvent and the excess of thionyl chloride were rotoevaporated to yield the crude chloromethyl derivative . The material obtained is sufficiently pure for further reaction.

To a solution of sodium ethoxide (30 mmol) prepared from sodium (0.69 g) in absolute ethanol (60 ml), was added a solution of phenol or thiophenol (33 mmol) in absolute ethanol (30 ml), then the crude chloromethyl derivative and potassium iodide (0.5 g, 3 mmol). The mixture was refluxed overnight, ethanol was removed and ice water added to the residue. The aqueous solution was acidified with concentrated hydrochloric acid and extracted with ether. The organic layer was washed with 10% sodium hydrogenosulfite, dried (Na_2SO_4) and then evaporated *in vacuo* to yield a residue to which 2N aqueous potassium hydroxide (30 ml) was added. The mixture was refluxed for 6 h cooled and acidified with concentrated hydrochloric acid. The acid (2) or (3) was collected by filtration and was utilized without purification in the next step.

A mixture of the crude acid (2) or (3) and polyphosphoric acid (H_3PO_4/P_2O_5 = 1/1, 150 g) was stirred at 100°C for 3 h (2a,b and 3a) or 16 h (2c). The resultant mixture was poured into crushed ice and extracted with methylene chloride. The organic layer was washed with 10% potassium carbonate and dried (Na_2SO_4). After evaporation of the solvent, pure compound (4) or (5) was obtained by column chromatography on silica gel, using methylene chloride as eluent (Table 2).

3-(Phenylthiomethyl)isoxazol-5(*4H*)-one (10)

To a solution of hydroxylamine hydrochloride (0.7 g, 10 mmol) in water (3 ml) was added aniline (0.93 g, 10 mmol), ethyl 3-oxo-4-(phenylthio)butanoate (8)[25] (2.38 g, 10 mmol) and methanol (20 ml) The solution was allowed to stand at room temperature for 2 h. After evaporation of methanol, the residue was dissolved in 1N aqueous sodium hydroxide (20 ml). The solution was stirred for 10 min, extracted with methylene chloride and then acidified with concentrated hydrochloric acid. The crude isoxazolone (10) was collected by filtration (yield 58%). It was very difficult to purify and was routinely utilized without purification in the next step.

4-Acetyl-3-(phenoxymethyl)isoxazol-5(4*H*)-one (11a) and 4-Acetyl-3-(phenylthiomethyl)isoxazol-5(4*H*)-one (12a)

These compounds were prepared by acylation of compounds (9) and (10) with triethyl orthoacetate according to the literature method[17]. Analytical samples of compounds (11a) and (12a) were obtained by recrystallization from acetonitrile (Table 1).

4-Acyl-3-(phenoxymethyl)isoxazol-5(4*H*)-ones (11b,c)

These compounds were prepared by acylation of compound (9), using a mixture of propionic anhydride and sodium propionate or benzoic anhydride and sodium benzoate, according to the literature method[17,18]. Analytical samples were obtained by recrystallization from acetonitrile (11b) or ethanol (11c) (Table 1).

4*H*,10*H*[1]Benzoxepino[3,4-c]isoxazol-4-ones (15a-c) and 4*H*,10*H*[1]Benzothiepino[3,4-c]isoxazol-4-one (16a)

The acids (13) and (14) were prepared from (11) and (12) according to the literature method[17] described for the synthesis of 5-methyl-3-phenylisoxazole-4-carboxylic acid from 4-acetyl-3-phenylisoxazol-5(4*H*)-one except that the reflux time was 12 h, using 40% aqueous sodium hydroxide. Treatment of the acids (13) and (14) with polyphosphoric acid [3 h (13a,b and 14a) or 6 h (13c) at 100°C] and work up in a similar manner as described above for the synthesis of compounds (4) and (5) afforded pure compounds (15) or (16) (Table 2).

4*H*,10*H*[1]Benzothiepino[4,3-*d*]isoxazol-4-one-1,1-dioxide (6a) and 4*H*,10*H*[1]Benzothiepino[3,4-c]isoxazol-4-one-1,1-dioxide (17a)

A solution of *m*-chloroperbenzoic acid (3.45 g, 20 mmol) in methylene chloride (40 ml) was added dropwise under nitrogen to a solution of benzothiepinoisoxazolone (5a) or (16a) (10 mmol) in methylene chloride (40 ml) at 0°C. The reaction mixture was stirred overnight at room temperature and then washed with 5% sodium hydrogenocarbonate and water. The organic layer was dried (Na_2SO_4) and the solvent was removed *in vacuo* to yield compound (6a) or (17a). Analytical samples were obtained by recrystallization from acetonitrile (Table 2).

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