Pergamon

Tetrahedron 58 (2002) 8719–8727

TETRAHEDRON

Studies directed to the synthesis of new C-5 spiroannulated julolidines

Alirio Palma,[a] Javier Silva Agredo,[a] Claudia Carrillo,[a] Vladimir Kouznetsov,[a,*] Elena Stashenko,[a] Alí Bahsas[b] and Juan Amaro-Luis[b]

[a]*Laboratory of Fine Organic Synthesis, Research Center for Biomolecules, School of Chemistry, Industrial University of Santander, A.A. 678, Bucaramanga, Colombia*

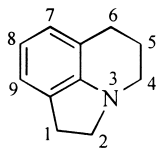
[b]*Laboratorio de RMN, Grupo de Productos Naturales, Departamento de Química, Universidad de los Andes, Mérida 5101, Venezuela*

Received 4 March 2002; revised 27 August 2002; accepted 28 August 2002

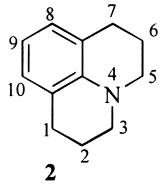
Abstract—Two series of new 7,9-disubstituted spirojulolidines **8a–d** and **10a–e** were synthesized by acid catalyzed intramolecular cyclization of *N*-(3-chloropropanoyl) spirodihydroquinolines **5a–d** and *N*-carbethoxymethyl spirodihydroquinolines **7a–e** using $AlCl_3$ and PPA, respectively. The spectroscopic analyses of intermediate compounds and the final spirojulolidines were discussed.

1. Introduction

The skeletons of the tricyclic compounds of the 1,2,5,6-tetrahydro-4*H*-pyrrolo[3,2,1-*ij*]quinoline and 2,3,6,7-tetrahydro-1*H*,5*H*-benzo[*ij*]quinolizine systems appear as a basic structural moieties in lilolidine **1**[1] and julolidine **2**[2] alkaloids. Their derivatives present very interesting scientific and industrial applications.[3–10]



1



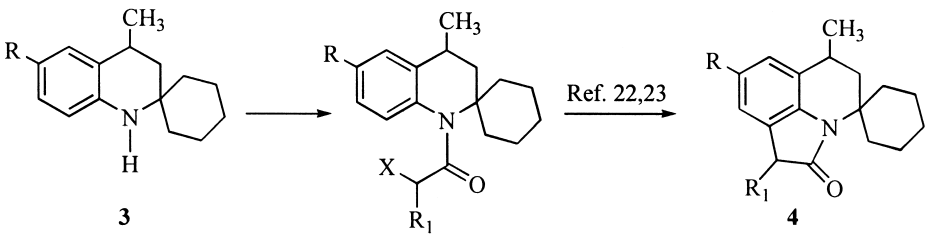
2

The syntheses and biological activities of 2-oxolilolidines as well as 4-oxo- and 6-oxolilolidines have been extensively studied.[11–15] During the last years, julolidine derivatives have attracted considerable attention of many research groups because of their broad-ranging biological activities. Some of them act as potential antidepressants and tranquilizers,[16] and as bifunctional intercalators for DNA.[17]

The most general and facile routes to lilolidine and julolidine skeletons employ tetrahydroquinoline or aniline derivatives as starting materials by way of *N*-alkylation followed by intramolecular electrophilic cyclization.[18,19] More recently, Professor Katritzky reported a convenient synthesis of julolidine derivatives in high yields by benzotriazole methodology.[20,21]

In connection with our studies on the synthesis of spirotetracyclic systems containing the dihydroquinoline skeleton **3** as a basic structural unit, we have recently synthesized spiro analogs of 2-oxolilolidine **4**[22,23] (Scheme 1).

Using this approach, we applied this type of intramolecular electrophilic cyclization to the synthesis of new 3-oxo-spirojulolidines **8** and 1-oxospirolilolidines **9** from

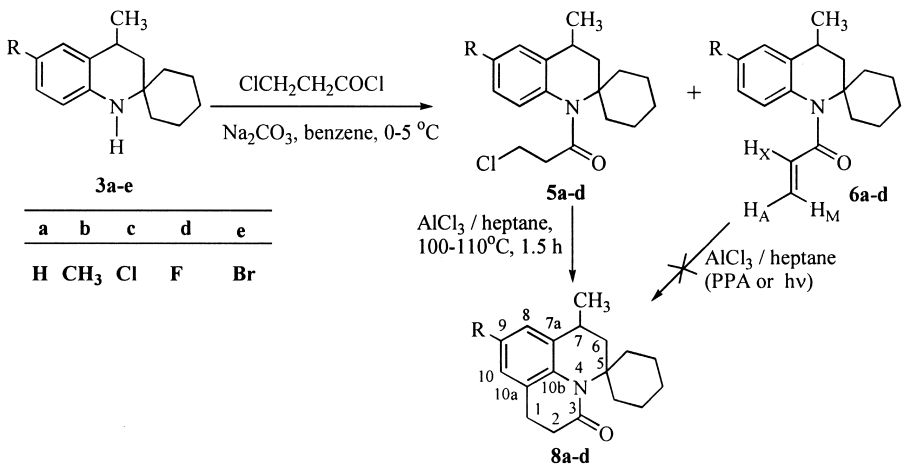


Scheme 1.

Keywords: spirolilolidine; spirojulolidine; intramolecular Friedel–Crafts alkylation.

* Corresponding author. Tel.: +5776-34-90-69; fax: +57-76-358210; e-mail: kouznet@uis.edu.co

0040–4020/02/$ - see front matter
PII: S0040-4020(02)01095-5



Scheme 2.

N-(3-chloropropanoyl) spirodihydroquinolines **5** and *N*-carbethoxymethyl spirodihydroquinolines **7**, according to Schemes 2 and 3, respectively.

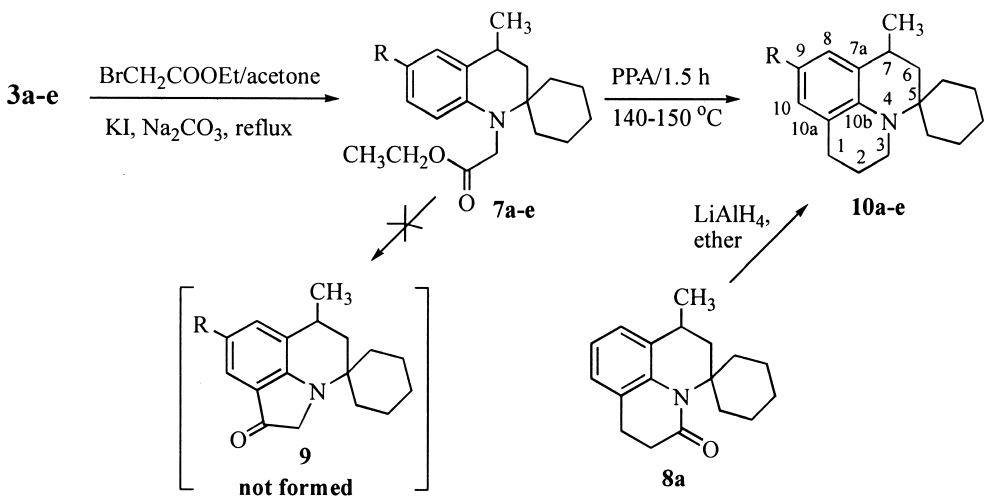
In this paper, we report results obtained in both the classical and our alternative[24] methodologies for the conversion of these *N*-substituted spirodihidroquinolines under acidic conditions into new 7,9-disubstituted spirojulolidines **9** and **10** whose ring system have not been hitherto described completely.

Intramolecular Friedel–Crafts reactions promoted by Brönsted and Lewis acids are powerful methods for rapid construction of carbocyclic and heterocyclic compounds.[25,26] In our own work, we have exploited this classical methodology towards the construction of spiroheterocycles such as quinoline,[27–29] benzazepine,[30–32] and lilolidine[22,23] rings, using appropriate *gem*-γ-allyl-γ-aryl(benzyl)amino-cycloalkanes and *N*-substituted spirodihydroquinolines as starting materials.

2. Results and discussion

Our initial study starts with preparing *N*-(3-chloropropanoyl) spirodihydroquinolines **5** (Scheme 2). We expected that the procedure previously used by us for the preparation of *N*-[2-halogenopropanoyl(ethanoyl)] spirodihydroquinolines[22,23] would be applicable here to prepare **5**. However, when spiranes **3a** and **3d** were subjected to the usual conditions for N-acylation[22] (1.1 equiv. $ClCH_2CH_2COCl$/1.1 equiv. Et_3N/dry benzene/10°C) the products isolated were α,β-unsaturated amides **6a** and **6d**. The formation of these α,β-unsaturated amides was assumed to proceed via initial N-acylation with production of the expected *N*-(3-chloropropanoyl) spirodihydroquinolines **5a** and **5d** followed by their dehydrochlorination process catalyzed by Et_3N present in the reaction mixture.[33] The preparation of the desired compounds **5** eventually was partially solved running the acylation reaction in dry benzene in the presence of Na_2CO_3 at 0–5°C. Under these reaction conditions the amides **5a–d** were obtained as the major products in 19–65% overall yields, together with a significant amounts of unsaturated amides **6a–d** (16–28%), and unreacted starting materials (20–45%). The amides **5** and **6** were successfully separated by silica gel column chromatography.

The structures of **5** and **6** were confirmed by high resolution NMR spectroscopy. In the case of compounds **5a–d**, the methylenic protons $COCH_2$– resonate at 2.47–2.59 and 2.70–2.84 ppm as a doublet of doublet of doublet and



Scheme 3.

Table 1. ^{1}H and ^{13}C NMR spectral data of compounds **5a–d** and **8a–d**

No	^{1}H NMR ($CDCl_3$/TMS/400 MHz) δ (ppm), J (Hz)	^{13}C NMR ($CDCl_3$/TMS/100 MHz) δ (ppm)
5a	0.98 (1H, t, J=11.6 Hz, H_{ax}-3), 1.19–1.76, 3.01 (10H, m, $(CH_2)_5$), 1.35 (3H, d, J=6.8 Hz, 4-CH_3), 2.36 (1H, dd, J=3.4, 12.9 Hz, H_{eq}-3), 2.59 (1H, ddd, J=5.8, 8.5, 14.8 Hz, CO–CH_B), 2.73 (1H, m, H-4), 2.84 (1H, dt, J=5.7, 15.4 Hz, CO–CH_A), 3.69 (1H, dt, J=5.8, 10.6 Hz, Cl–CH_B), 3.81 (1H, ddd, J=5.8, 8.1, 10.6 Hz, Cl–CH_A), 6.93 (1H, d, J=6.9 Hz, H-8), 7.08 (1H, t, J=7.0 Hz, H-6), 7.18 (1H, t, J=7.0 Hz, H-7), 7.20 (1H, dd, J=1.2, 6.4 Hz, H-5)	17.2 (4-*C*H_3), 23.0–25.1 (*C*-cyclohexane), 29.1 (C-4), 40.9 (-*C*H_2–C=O), 41.4 (Cl–*C*H_2–), 44.8 (C-3), 63.7 (C-2), 123.3 (C-8), 125.6 (C-6), 125.8 (C-5), 125.9 (C-7), 139.1 (C-4a), 141.3 (C-8a), 171.4 (C=O)
5b	0.92 (1H, dd, J=12.6 Hz, H_{ax}-3), 1.18–1.75, 3.05 (10H, m, $(CH_2)_5$), 1.34 (3H, d, J=7.0 Hz, 4-CH_3), 2.35 (3H, s, 6-CH_3), 2.39 (1H, dd, J=2.8, 12.6 Hz, H_{eq}-3), 2.58 (1H, ddd, J=5.5, 8.0, 14.9 Hz, CO–CH_B), 2.70 (1H, m, H-4), 2.82 (1H, dt, J=6.0, 15.4 Hz, CO–CH_A), 3.68 (1H, dt, J=5.5, 10.9 Hz, Cl–CH_B), 3.78 (1H, ddd, J=5.5, 8.0, 10.9 Hz, Cl–CH_A), 6.82 (1H, d, J=7.8 Hz, H-8), 6.98 (1H, d, J=7.8 Hz, H-7), 7.00 (1H, s, H-5)	17.2 (4-*C*H_3), 21.2 (6-*C*H_3), 23.0–28.8 (*C*-cyclohexane), 29.1 (C-4), 40.8 (-*C*H_2–C=O), 41.4 (Cl–*C*H_2–), 44.9 (C-3), 63.5 (C-2), 123.5 (C-8), 124.2 (C-6), 125.6 (C-5), 126.4 (C-7), 136.1 (C-4a), 140.7 (C-8a), 171.3 (C=O)
5c	0.97 (1H, t, J=12.0 Hz, H_{ax}-3), 1.15–1.77, 3.06 (10H, m, $(CH_2)_5$), 1.34 (3H, d, J=6.8 Hz, 4-CH_3), 2.37 (1H, dd, J=3.5, 13.0 Hz, H_{eq}-3), 2.57 (1H, ddd, J=5.8, 8.4, 15.1 Hz, CO–CH_B), 2.71 (1H, m, H-4), 2.82 (1H, dt, J=5.8, 15.1 Hz, CO–CH_A), 3.69 (1H, dt, J=5.8, 10.6 Hz, Cl–CH_B), 3.80 (1H, ddd, J=5.7, 8.2, 10.6 Hz, Cl–CH_A), 6.87 (1H, d, J=8.2 Hz, H-8), 7.13 (1H, d, J=8.2 Hz, H-7), 7.18 (1H, s, H-5)	17.2 (4-*C*H_3), 23.8–25.0 (*C*-cyclohexane), 29.3 (C-4), 40.7 (–*C*H_2–C=O), 41.3 (Cl–*C*H_2–), 44.5 (C-3), 63.9 (C-2), 123.8 (C-8), 126.0 (C-6), 126.7 (C-5), 131.3 (C-7), 137.7 (C-4a), 143.1 (C-8a), 171.3 (C=O)
5d	0.87 (1H, dd, J=13.2 Hz, H_{ax}-3), 1.15–1.69, 3.03 (10H, m, $(CH_2)_5$), 1.26 (3H, d, J=6.8 Hz, 4-CH_3), 2.28 (1H, dd, J=3.5, 13.1 Hz, H_{eq}-3), 2.47 (1H, ddd, J=6.3, 8.4, 15.0 Hz, CO–CH_B), 2.62 (1H, m, H-4), 2.70 (1H, dt, J=6.0, 15.2 Hz, CO–CH_A), 3.62 (1H, dt, J=5.8, 10.9 Hz, Cl–CH_B), 3.71 (1H, ddd, J=5.6, 8.3, 10.6 Hz, Cl–CH_A), 6.73 (1H, d, J=8.0 Hz, H-8), 6.84 (1H, d, J=8.5 Hz, H-5), 7.79 (1H, t, J=8.5 Hz, H-7)	16.9 (4-*C*H_3), 23.8–25.0 (*C*-cyclohexane), 29.4 (C-4), 40.6 (–*C*H_2–C=O), 41.3 (Cl–*C*H_2–), 44.5 (C-3), 63.7 (C-2), 125.4 (C-8), 127.6 (C-5), 127.7 (C-7), 133.5 (C-4a), 143.2 (C-8a), 143.7 (C-6), 171.1 (C=O)
8a	1.09 (1H, dd, J=12.9 Hz, H_{ax}-6), 1.20–1.73, 3.17 (10H, m, $(CH_2)_5$), 1.35 (3H, d, J=6.0 Hz, 7-CH_3), 2.51 (1H, dd, J=6.2, 14.0 Hz, H_{eq}-6), 2.53 (2H, m, H-2), 2.65 (1H, dddd, J=3.8, 13.5, 14.9 Hz, H_{ax}-1), 2.75 (1H, m, H-7), 2.89 (1H, dt, J=3.8, 15.0 Hz, H_{eq}-1), 6.93 (1H, t, J=7.2 Hz, H-9), 6.98 (1H, d, J=6.8 Hz, H-10), 7.08 (1H, d, J=7.2 Hz, H-8)	18.8 (7-*C*H_3), 23.1–35.5 (*C*-cyclohexane), 25.9 (C-7), 26.6 (C-1), 35.6 (C-2), 41.6 (C-6), 61.8 (C-5), 122.1 (C-9), 125.3 (C-8), 125.7 (C-10), 127.7 (C-10a), 133.9 (C-7a), 138.1 (C-10b), 171.5 (C=O)
8b	0.99 (1H, t, J=13.6 Hz, H_{ax}-6), 1.17–1.59, 3.12 (10H, m, $(CH_2)_5$), 1.25 (3H, d, J=6.7 Hz, 7-CH_3), 2.39 (1H, dd, J=5.0, 14.0 Hz, H_{eq}-6), 2.45 (2H, m, H-2), 2.53 (1H, dddd, J=5.2, 14.0, 14.9 Hz, H_{ax}-1), 2.63 (1H, m, H-7), 2.78 (1H, dt, J=5.0, 15.0 Hz, H_{eq}-1), 6.71 (1H, s, H-10), 6.79 (1H, s, H-8)	18.7 (7-*C*H_3), 20.6 (9-CH_3), 23.0–35.3 (*C*-cyclohexane), 25.8 (C-7), 26.4 (C-1), 35.7 (C-2), 41.6 (C-6), 61.5 (C-5), 123.2 (C-10), 125.9 (C-8), 127.5 (C-10a), 131.4 (C-10b), 133.6 (C-7a), 135.5 (C-9), 171.3 (C=O)
8c	1.03 (1H, t, J=13.5 Hz, H_{ax}-6), 1.20–2.00, 3.10, 3.38 (10H, m, $(CH_2)_5$), 1.31 (3H, d, J=7.2 Hz, 7-CH_3), 2.40 (1H, dd, J=5.5, 14.0 Hz, H_{eq}-6), 2.50 (2H, m, H-2), 2.60 (1H, dddd, J=5.3, 15.3, 15.6 Hz, H_{ax}-1), 2.65 (1H, m, H-7), 2.82 (1H, dt, J=15.3, 15.3 Hz, H_{eq}-1), 6.98 (1H, s, H-10), 7.06 (1H, s, H-8)	18.5 (7-*C*H_3), 22.9–35.3 (*C*-cyclohexane), 21.8 (C-7), 26.6 (C-1), 31.1 (C-2), 41.3 (C-6), 61.8 (C-5), 121.3 (C-10), 124.1 (C-8), 127.0 (C-10b), 129.3 (C-10a), 135.5 (C-7a), 136.5 (C-9), 170.9 (C=O)
8d	0.98 (1H, t, J=13.9 Hz, H_{ax}-6), 0.86–1.70, 3.08 (10H, m, $(CH_2)_5$), 1.26 (3H, d, J=6.7 Hz, 7-CH_3), 2.38 (1H, dd, J=5.5, 14.2 Hz, H_{eq}-6), 2.45 (2H, m, H-2), 2.55 (1H, dddd, J=5.3, 14.9, 15.2 Hz, H_{ax}-1), 2.63 (1H, m, H-7), 2.78 (1H, dt, J=4.8, 15.3 Hz, H_{eq}-1), 6.59 (1H, dd, J=2.8, 8.1 Hz, H-10), 6.67 (1H, dd, J=2.8, 9.5 Hz, H-8)	18.5 (7-*C*H_3), 23.0–35.1 (*C*-cyclohexane), 25.8 (C-7), 26.7 (C-1), 35.2 (C-2), 41.3 (C-6), 61.7 (C-5), 109.4 (C-10), 111.6 (C-8), 134.1 (C-9), 135.9 (C-7a), 156.7 (C-10a), 159.2 (C-10b), 170.9 (C=O)

doublet of triplet. In addition, a one-proton doublet of triplet at 3.62–3.69 ppm and one-proton doublet of doublet of doublet at 3.71–3.81 ppm were indicated, respectively, to the terminal –*C*H_2Cl protons (Table 1). On the other hand, the ^{1}H NMR spectra of compounds **6a–d** show three set of characteristic signals from a vinyl protons of the amide fragment CH_AH_M=CH_X–C=O, respectively, at 5.38–5.43 ppm (dd, H_X), 5.97–6.08 ppm (dd, H_A), and 6.21–6.30 ppm (dd, H_M). Such a large downfield shift of the H_M signal is due to the anisotropic effect of carbonyl group, and consequently it can be considered therefore that CH_AH_M=CH_X–C=O fragment adopts the *cis* conformation.

In the next step of our study, using the classical approach, we finished the synthesis of the 3-oxospirojulolidines **8a–d** from the compounds **5a–d** by heating in heptane with aluminum chloride (Scheme 2). New spirojulolidones **8a–d** were isolated by silica gel column chromatography in 61–85% yield as colorless crystalline substances.

The ^{13}C NMR and DEPT-135 spectra indicated the presence of eight CH_2, one CH, and one quaternary sp^3-carbon signals at medium and high fields. The combination of 1D and 2D NMR spectroscopy achieved complete elucidation of the compounds **8**.

The coupling pattern of the ^{1}H NMR spectra is characteristic of a trisubstituted (compound **8a**) or tetrasubstituted benzene derivative. These exhibit aromatic proton NMR absorption peaks at 6.67–7.08 ppm (H-8), 6.93 ppm (H-9), and 6.59–6.98 ppm (H-10), and carbon-13 absorptions at 133.6–135.9 ppm (C-7a), 111.6–125.9 ppm (C-8), 122.1–136.5 ppm (C-9), 109.4–125.7 ppm (C-10), 127.7–156.7 ppm (C-10a), 127.0–159.2 ppm (C-10b), and carbonyl carbon absorption at 170.9–171.5 ppm (Table 1). The lactam structure of compounds **8** was also supported by the IR spectra in which an amide carbonyl vibration band was evident at 1670–1661 cm^{-1}.

It should be noted that repeated attempts to cyclize the α,β-unsaturated amides **6a–d** either by heating in the presence of $AlCl_3$ or polyphosphoric acid (PPA)[34] or by UV irradiation[35] were quite unsuccessful.

Thus, we focused our attention on the synthesis of the

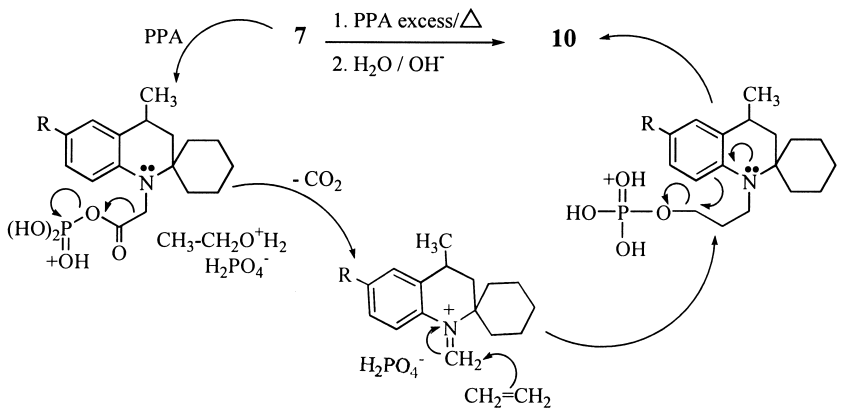
Table 2. ^{1}H and ^{13}C NMR spectral data of compounds **7a–e** and **10a–e**

No	^{1}H NMR ($CDCl_3$/TMS/400 MHz) δ (ppm), J (Hz)	^{13}C NMR ($CDCl_3$/TMS/100 MHz) δ (ppm)
7a	1.20–1.82 (10H, m, $(CH_2)_5$), 1.27 (3H, t, J=7.1 Hz, CH_3–CH_2–), 1.32 (1H, t, J=14.3 Hz, H_{ax}-3), 1.35 (3H, d, J=6.7 Hz, 4-CH_3), 2.37 (1H, dd, J=4.3, 13.3 Hz, H_{eq}-3), 2.82 (1H, m, H-4), 3.86 (1H, d, J=18.5 Hz, N–CH_B), 4.20 (1H, d, J=18.5 Hz, N–CH_A), 4.22 (2H, q, OCH_2), 6.32 (1H, d, J=8.4 Hz, H-8), 6.65 (1H, t, J=7.7 Hz, H-6), 7.03 (1H, t, J=7.9 Hz, H-7), 7.13 (1H, dd, J=1.2, 7.5 Hz, H-5)	14.2 (CH_3–CH_2–), 20.0 (4-CH_3), 22.2–37.6 (*C*-cyclohexane), 26.3 (C-4), 38.6 (C-3), 46.9 (N–CH_2), 57.2 (C-2), 60.9 (O–CH_2), 111.3 (C-8), 116.2 (C-6), 125.6 (C-5), 126.9 (C-7), 128.0 (C-4a), 145.1 (C-8a), 172.5 (C=O)
7b	1.18–1.66 (10H, m, $(CH_2)_5$), 1.26 (3H, t, J=7.1 Hz, CH_3–CH_2–), 1.35 (3H, d, J=6.6 Hz, 4-CH_3), 2.35 (3H, s, 6-CH_3), 2.39 (1H, dd, J=4.1, 13.4 Hz, H_{eq}-3), 2.72 (1H, m, H-4), 3.76 (1H, d, J=18.3 Hz, N–CH_B), 4.17 (2H, q, OCH_2), 4.18 (1H, d, J=18.3 Hz, N–CH_A), 6.25 (1H, d, J=8.0 Hz, H-8), 6.88 (1H, d, J=8.4 Hz, H-7), 6.92 (1H, s, H-5)	14.2 (CH_3–CH_2–), 20.1 (4-CH_3), 23.0 (6-CH_3), 22.1–37.2 (*C*-cyclohexane), 38.7 (C-3), 26.6 (C-4), 57.3 (C-2), 46.9 (N–CH_2), 60.3 (O–CH_2), 111.4 (C-8), 116.4 (C-6), 128.8 (C-5), 130.8 (C-7), 132.3 (C-4a), 141.4 (C-8a), 167.7 (C=O)
7c	1.15–1.68 (10H, m, $(CH_2)_5$), 1.19 (3H, t, J=7.0 Hz, CH_3–CH_2–), 1.25 (3H, d, J=6.6 Hz, 4-CH_3), 2.28 (1H, dd, J=4.0, 13.6 Hz, H_{eq}-3), 2.70 (1H, m, H-4), 3.76 (1H, d, J=18.6 Hz, N–CH_B), 4.10 (2H, q, OCH_2), 4.11 (1H, d, J=18.6 Hz, N–CH_A), 6.14 (1H, d, J=8.5 Hz, H-8), 6.88 (1H, dd, J=2.3, 8.6 Hz, H-7), 6.99 (1H, s, H-5)	14.2 (CH_3–CH_2–), 19.8 (4-CH_3), 22.1–37.3 (*C*-cyclohexane), 26.3 (C-4), 38.2 (C-3), 46.6 (N–CH_2), 57.3 (C-2), 60.9 (O–CH_2), 112.2 (C-8), 121.0 (C-6), 125.5 (C-5), 126.4 (C-7), 129.8 (C-4a), 143.6 (C-8a), 171.9 (C=O)
7d	1.23–1.74 (10H, m, $(CH_2)_5$), 1.25 (3H, t, J=7.0 Hz, CH_3–CH_2–), 1.30 (3H, d, J=7.0 Hz, 4-CH_3), 2.34 (1H, dd, J=4.0, 13.1 Hz, H_{eq}-3), 2.77 (1H, m, H-4), 3.82 (1H, d, J=18.1 Hz, N–CH_B), 4.15 (1H, d, J=18.1 Hz, N–CH_A), 4.17 (2H, q, OCH_2), 6.20 (1H, dd, J=4.6, 9.1 Hz, H-8), 6.70 (1H, td, J=2.5, 8.6 Hz, H-7), 6.83 (1H, d, J=10.1 Hz, H-5)	14.2 (CH_3–CH_2–), 19.9 (4-CH_3), 22.2–37.4 (*C*-cyclohexane), 26.5 (C-4), 38.4 (C-3), 47.1 (N–CH_2), 57.1 (C-2), 60.9 (O–CH_2), 111.8 (C-8), 112.6 (C-5), 112.9 (C-7), 129.9 (C-4a), 141.4 (C-8a), 156.3 (C-6), 172.4 (C=O)
7e	1.21–1.72 (10H, m, $(CH_2)_5$), 1.25 (3H, t, J=7.1 Hz, CH_3–CH_2–), 1.31 (3H, d, J=6.6 Hz, 4-CH_3), 2.34 (1H, dd, J=4.0, 13.1 Hz, H_{eq}-3), 2.77 (1H, m, H-4), 3.82 (1H, d, J=18.1 Hz, N–CH_B), 4.16 (1H, d, J=18.1 Hz, N–CH_A), 4.17 (2H, q, OCH_2), 6.16 (1H, d, J=8.5 Hz, H-8), 7.07 (1H, dd, J=2.0, 8.6 Hz, H-7), 7.17 (1H, s, H-5)	14.2 (CH_3–CH_2–), 19.8 (4-CH_3), 22.1–37.3 (*C*-cyclohexane), 26.3 (C-4), 38.2 (C-3), 46.6 (N–CH_2), 57.4 (C-2), 61.0 (O–CH_2), 108.3 (C-6), 112.8 (C-8), 128.3 (C-5), 129.4 (C-7), 130.3 (C-4a), 144.0 (C-8a), 171.9 (C=O)
10a	1.16–1.90 (10H, m, $(CH_2)_5$), 1.19 (1H, t, J=12.6 Hz, H_{ax}-6), 1.34 (3H, d, J=6.6 Hz, 7-CH_3), 1.95 (2H, td, J=4.0, 13.1 Hz, H-2), 2.36 (1H, dd, J=4.5, 13.1 Hz, H_{eq}-6), 2.76 (2H, m, H-1), 2.77 (1H, m, H-7), 3.08 (1H, ddd, J=4.3, 7.6, 11.8 Hz, H_{ax}-3), 3.45 (1H, dt, J=5.0, 10.6 Hz, H_{eq}-3), 6.44 (1H, t, J=7.6 Hz, H-9), 6.83 (1H, d, J=7.0 Hz, H-10), 6.97 (1H, d, J=7.6 Hz, H-8)	20.3 (7-CH_3), 22.2–30.5 (*C*-cyclohexane), 26.6 (C-7), 28.5 (C-1), 36.3 (C-2), 39.1 (C-6), 41.3 (C-3), 56.5 (C-5), 114.9 (C-9), 122.0 (C-10a), 123.4 (C-8), 127.3 (C-10), 127.9 (C-7a), 142.6 (C-10b)
10b	1.05–1.80 (10H, m, $(CH_2)_5$), 1.09 (1H, t, J=12.6 Hz, H_{ax}-6), 1.24 (3H, d, J=6.6 Hz, 7-CH_3), 1.87 (2H, td, J=4.0, 13.1 Hz, H-2), 2.25 (1H, dd, J=4.5, 13.1 Hz, H_{eq}-6), 2.61 (2H, m, H-1), 2.63 (1H, m, H-7), 2.92 (1H, ddd, J=3.8, 8.3, 11.8 Hz, H_{ax}-3), 3.36 (1H, dt, J=5.5, 10.1 Hz, H_{eq}-3), 6.57 (1H, s, H-10), 6.70 (1H, s, H-8)	20.8 (7-CH_3), 20.9 (9-CH_3), 21.0–30.5 (*C*-cyclohexane), 27.0 (C-7), 28.8 (C-1), 36.6 (C-2), 39.7 (C-6), 41.6 (C-3), 56.6 (C-5), 124.4 (C-9), 124.6 (C-8), 127.7 (C-10a), 128.3 (C-10), 128.4 (C-7a), 140.6 (C-10b)
10c	1.08–1.83 (10H, m, $(CH_2)_5$), 1.12 (1H, t, J=13.1 Hz, H_{ax}-6), 1.28 (3H, d, J=6.8 Hz, 7-CH_3), 1.92 (2H, td, J=4.0, 13.1 Hz, H-2), 2.32 (1H, dd, J=4.8, 13.3 Hz, H_{eq}-6), 2.67 (2H, m, H-1), 2.68 (1H, m, H-7), 3.00 (1H, ddd, J=4.3, 8.6, 11.6 Hz, H_{ax}-3), 3.41 (1H, dt, J=5.0, 11.1 Hz, H_{eq}-3), 6.75 (1H, s, H-10), 6.87 (1H, s, H-8)	20.2 (7-CH_3), 22.1–30.4 (*C*-cyclohexane), 26.7 (C-7), 28.3 (C-1), 36.2 (C-2), 38.9 (C-6), 41.2 (C-3), 56.6 (C-5), 119.6 (C-9), 123.3 (C-8), 123.7 (C-10a), 126.6 (C-10), 129.7 (C-7a), 141.1 (C-10b)
10d	1.03–1.89 (10H, m, $(CH_2)_5$), 1.06 (1H, t, J=13.1 Hz, H_{ax}-6), 1.22 (3H, d, J=6.5 Hz, 7-CH_3), 1.86 (2H, td, J=4.0, 13.1 Hz, H-2), 2.26 (1H, dd, J=5.0, 13.1 Hz, H_{eq}-6), 2.61 (2H, m, H-1), 2.63 (1H, m, H-7), 2.88 (1H, ddd, J=3.0, 9.1, 12.1 Hz, H_{ax}-3), 3.37 (1H, dt, J=5.8, 10.1 Hz, H_{eq}-3), 6.46 (1H, d, J=6.6 Hz, H-10), 6.60 (1H, d, J=9.6 Hz, H-8)	20.6 (7-CH_3), 22.6–30.5 (*C*-cyclohexane), 27.3 (C-7), 28.8 (C-1), 36.5 (C-2), 39.5 (C-6), 41.5 (C-3), 56.8 (C-5), 110.5 (C-8), 113.4 (C-10), 130.1 (C-10a), 130.2 (C-7a), 139.2 (C-10b), 155.9 (C-9)
10e	1.05–1.80 (10H, m, $(CH_2)_5$), 1.07 (1H, t, J=12.6 Hz, H_{ax}-6), 1.22 (3H, d, J=6.5 Hz, 7-CH_3), 1.87 (2H, td, J=4.0, 13.1 Hz, H-2), 2.12 (3H, s, 9-CH_3), 2.26 (1H, dd, J=4.5, 13.6 Hz, H_{eq}-6), 2.60 (2H, m, H-1), 2.61 (1H, m, H-7), 2.95 (1H, ddd, J=3.8, 8.1, 11.8 Hz, H_{ax}-3), 3.34 (1H, dt, J=4.8, 10.6 Hz, H_{eq}-3), 6.83 (1H, s, H-10), 6.93 (1H, s, H-8)	20.2 (7-CH_3), 22.1–30.4 (*C*-cyclohexane), 28.3 (C-1), 26.7 (C-7), 36.2 (C-2), 38.9 (C-6), 41.2 (C-3), 56.7 (C-5), 106.9 (C-9), 124.2 (C-10a), 126.1 (C-8), 129.5 (C-10), 130.2 (C-7a), 141.6 (C-10b)

desired 1-oxospirolilolidines **9**. As outlined in Scheme 3, our approach to the above-mentioned compounds also started from spirodihydroquinolines **3**. After compounds **3a–e** were *N*-carbethoxymethylated, the resulting *N*-alkylated compounds **7a–e** were formed in 56–79% yields, and NH-spirodihydroquinolines were recovered in 20–35%. Compounds **7a–e** were easily isolated from the reaction mixture by alumina column chromatography as maroon oils. All attempts to further improve the yields of **7** by extending the reaction time or by using different solvents (benzene, DMF) met with failure.

The IR spectra of these compounds revealed intense peaks at 1728–1726 and 1754–1752 cm^{-1} characteristics for the carbonyl stretch of ester group, and the ^{1}H NMR spectra showed the same set of signals in the aromatic and aliphatic (cyclohexane protons and H_{ax}-3, H_{eq}-3 and H-4 protons) regions as those reported for **6a–d**, it differed in the presence of signals originating from the protons of the *N*-carbethoxymethyl fragment, which resonated in high and medium field as a triplet, a quartet and a doublet of doublets, respectively (Table 2).

Finally, after the acidic treatment of **7a–e** with PPA at 140–150°C did not give structure **9**, but gave, to our surprise, the unexpected spirojulolidines **10a–e**. Under these reaction conditions, the spirojulolidines **10a–e** were obtained in 50–62% yields as red oils after NaOH work-up of the reaction mixture, extraction and alumina chromatography purification. In all cases, the expected 1-oxospirolilolidines



Scheme 4.

9 have not been detected. It is noteworthy, that attempted cyclization of **7** in the presence of concentrated H_2SO_4 led to decomposition.

These final synthetic results needed to be corroborated either by detailed spectroscopic analysis or chemical methods. First of all, the absence of a carbonyl band absorption in their IR spectra is a very strong evidence of julolidine ring formation. The isolated substances with *m/z* 255, 269, 289, 273 and 335 were initially thought to be the spirolilolidones **9**, but these structures were readily excluded on the basis of their NMR spectra.

The ^1H and ^{13}C NMR data and 2D experiments allowed an unambiguous assignment of the formation of the julolidine ring. Thus, the ^1H NMR spectra displayed the signals of three (for compound **10a**) or two (for compounds **10b**–**e**) aromatic protons. The six aliphatic protons of the three-methylene groups of the new piperidine ring appeared as a one-proton doublet of triplet for H_{eq}-3 (3.36–3.45 ppm) and one-proton doublet of doublet of doublet for H_{ax}-3 (2.88–3.08 ppm), as a two-proton multiplet for H-1 (2.60–2.76 ppm), and as a two-proton triplet of doublet for H-2 (1.86–1.95 ppm). Furthermore, the chemical shifts of the skeletal ^{13}C nuclei were consistent with the proposed tetracyclic structures. Accordingly, four quaternary aromatic carbons (three for compound **10a**) as well as nine CH_2, one CH and one CH_3 signals at low and high fields were observed in the DEPT-135 experiments on compounds **10a**–**e** (Table 2). In all ^{13}C NMR spectra, a carbonyl group characteristic signal was absent, contrarily to the case of the closely related spirolactames **8a**–**d**.

Additionally, in the heteronuclear multiple bond coherence (HMBC) spectra, the H-1 signal was found to be ^2J, ^3J and ^4J coupled to the signals of C-10a (122.0–130.1 ppm), C-2 (36.2–36.6 ppm), C-10 (113.4–129.5 ppm), C-10b (139.2–142.6 ppm), C-3 (41.2–41.6 ppm), C-7a (127.9–130.2 ppm), and C-9 (106.9–155.9 ppm), respectively. In turn, the H-2 signal showed correlations with C-10a, C-10, C-10b and C-5 (56.5–56.8 ppm), respectively. The H-3 signal also revealed ^2J, ^3J and ^4J long-range correlations with C-2, C-1 (28.5–28.8 ppm), C-10b, C-5, C-10a, C-7a and C-6 (38.9–39.7 ppm).

Moreover, treatment of **8a** with $LiAlH_4$ in dry ether[36] gave a product with molecular ion peak at *m/z* 255. NMR and IR analyses confirmed that the obtained product was the spirojulolidine **10a** (Scheme 3). This fact was the straightforward demonstration of the structures proposed for compounds **10**.

The central question was how the ester moiety reacted with PPA to give the observed products. Here, we try to give a mechanistic explanation on this interesting formation of **10** from **7** (Scheme 4). We suggest that under acidic conditions (excess of PPA, heating) the reaction could begin with the nucleophilic attack of the hydroxy group of PPA on the ester carbonyl group.[37] Resulted protonated species may produce ethanol which immediately reacts with excess of PPA with ethylene and iminium cation formation via decarboxylation. Subsequent electrophilic addition of iminium ion to incipient ethylene give rise the phosphoric ester with nonprotonated nitrogen atom. This last intermediate would accommodate the *ortho* intramolecular electrophilic aromatic substitution to form a saturated ring of julolidine ring.

3. Conclusions

In this study, we carried out the synthesis of 3-oxospirojulolidines, which had not been reported before. A new series of spirojulolidines was also synthesized with good yields by approach alternative to those previously reported in the literature. This novel synthesis of the julolidine ring system could well be general.

4. Experimental

4.1. General methods

IR spectra were obtained on a Nicolet Avatar 360-FTIR spectrometer as potassium bromide pellets. The ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ solution with TMS as internal standard on Bruker AM-400 spectrometer (400 MHz ^1H NMR and 100 MHz ^{13}C NMR). Chemical shifts are reported in ppm and coupling constants are in Hz. GC–MS spectra were obtained on a HP-5890A Series II gas chromatograph interfaced to a HP-5972 mass selective detector (MSD) with a HP MS ChemStation Data. The electron beam energy was 70 eV. Elemental analyses were

performed on a Perkin–Elmer 2400 Series II analyzer. Column chromatography and TLC were carried out using Merck Kieselgel 60 (230–400 mesh) or Merck aluminium oxide 90 active, neutral (activity I, 70–230 mesh) and Silufol UV_{54} chromatoplates. Melting points were measured using a Fisher–Johns melting point apparatus and are uncorrected. All reagents were purchased from Merck, Sigma and Aldrich Chemical Co. All solvents were used without further purification. Started spirodihydroquinolines **3** were synthesized according to our methodology.[22,27,28]

4.2. General procedure for the synthesis of *N*-(3-chloropropanoyl)-3,4-dihydro-4-methylspiro[quinoline-2,1′-cyclohexanes] 5a–d and *N*-(propen-2-oyl)-3,4-dihydro-4-methylspiro[quinoline-2,1′-cyclohexanes] 6a–d

To a stirred and cooled (0°C) solution of spiranes **3a–d** (1 mmol) and Na_2CO_3 (2 mmol) in dry benzene (15 ml), a solution (3 ml) of 3-chloropropanoyl chloride (1 mmol) in benzene was added dropwise for 10 min. After the addition was complete, the solution was stirred at 0–5°C for 30–42 h. and monitored by thin layer chromatography. The reaction mixture was then filtered and solvent evaporated in vacuo. The crude product was fractionated by chromatography on a silica gel column using heptane and heptane–ethyl acetate (15:1, 10:1, 5:1) as an eluents to give compounds **5a–d** and **6a–d**. The ^1H and ^{13}C NMR data of compounds **5a–d** are given in Table 1.

4.2.1. *N*-(3-Chloropropanoyl)-3,4-dihydro-4-methylspiro-[quinoline-2,1′-cyclohexane] 5a. This compound was isolated as colorless crystals; mp 72–73°C (from heptane); yield 34%; ν_{max} (KBr) (cm^{-1}) 1662 (C═O). Mass spectrum (EI): *m/z* (%) 305 (M^+, ^{35}Cl, 25), 290 (4), 270 (8), 263 (1), 249 (2), 215 (16), 210 (90), 209 (8), 200 (58), 172 (100), 170 (10), 144 (36). Anal. calcd for $C_{18}H_{24}ClNO$: C, 70.69; H, 7.91; N, 4.58%. Found: C, 70.48; H, 7.85; N, 4.61%.

4.2.2. *N*-(3-Chloropropanoyl)-3,4-dihydro-4,6-dimethylspiro[quinoline-2,1′-cyclohexane] 5b. This compound was isolated as maroon viscous oil; yield 65%; ν_{max} (KBr) (cm^{-1}) 1661 (C═O). Mass spectrum (EI): *m/z* (%) 319 ($M^{+\cdot}$, ^{35}Cl, 21), 304 (3), 284 (5), 277 (1), 263 (1), 229 (15), 224 (100), 223 (6), 214 (35), 186 (66), 184 (7), 158 (18). Anal. calcd for $C_{19}H_{26}ClNO$: C, 71.34; H, 8.19; N, 4.38%. Found: C, 71.46; H, 8.12; N, 4.32%.

4.2.3. 6-Chloro-*N*-(3-chloropropanoyl)-3,4-dihydro-4-methylspiro[quinoline-2,1′-cyclohexane] 5c. This compound was isolated as colorless crystals; mp 92–93°C (from heptane); yield 19%; ν_{max} (KBr) (cm^{-1}) 1661 (C═O). Mass spectrum (EI): *m/z* (%) 339 ($M^{+\cdot}$, ^{35}Cl, 29), 324 (3), 304 (8), 297 (1), 283 (2), 249 (29), 244 (96), 243 (11), 234 (60), 206 (100), 204 (7), 178 (22). Anal. calcd for $C_{18}H_{23}Cl_2NO$: C, 63.53; H, 6.81; N, 4.12%. Found: C, 63.41; H, 6.92; N, 4.03%.

4.2.4. *N*-(3-Chloropropanoyl)-3,4-dihydro-6-fluoro-4-methylspiro[quinoline-2,1′-cyclohexane] 5d. This compound was isolated as maroon viscous oil; yield 24%; ν_{max} (film) (cm^{-1}) 1661 (C═O). Mass spectrum (EI): *m/z* (%) 323 ($M^{+\cdot}$, ^{35}Cl, 30), 324 (3), 308 (8), 288 (8), 287 (1), 281 (1), 233 (14), 228 (70), 227 (8), 218 (50), 190 (100), 188 (12), 162 (32). Anal. calcd for $C_{18}H_{23}ClFNO$: C, 66.76; H, 7.16; N, 4.33%. Found: C, 66.61; H, 7.29; N, 4.18%.

4.2.5. *N*-(Propen-2-oyl)-3,4-dihydro-4-methylspiro[quinoline-2,1′-cyclohexane] 6a. This compound was isolated as colorless crystals; mp 86–87°C (from heptane); yield 28%; ν_{max} (KBr) (cm^{-1}) 1651 (C═O); ^1H NMR (400 MHz, $CDCl_3$) δ 0.95 (1H, t, J=13.0 Hz, H_{ax}-3), 1.20–1.90, 2.78, 3.10 (10H, m, $(CH_2)_5$), 1.35 (3H, d, J=6.6 Hz, 4-CH_3), 2.36 (1H, dd, J=3.4, 12.9 Hz, H_{eq}-3), 2.70 (1H, m, H-4), 5.43 (1H, dd, J=1.1, 10.1 Hz, H_X), 6.08 (1H, dd, J=10.2 Hz, H_A), 6.28 (1H, dd, J=1.2, 16.4 Hz, H_M), 6.95 (1H, d, J=6.9 Hz, H-8), 7.10 (1H, t, J=6.9 Hz, H-6), 7.16 (1H, t, J=7.0 Hz, H-7), 7.19 (1H, d, J=6.7 Hz, H-5). Mass spectrum (EI): *m/z* (%) 269 ($M^{+\cdot}$, 43), 254 (35), 226 (36), 174 (56), 173 (12), 160 (9), 158 (11), 148 (19), 146 (6), 132 (25), 55 (100). Anal. calcd for $C_{18}H_{23}NO$: C, 80.26; H, 8.61; N, 5.20%. Found: C, 80.13; H, 8.73; N, 5.09%.

4.2.6. *N*-(Propen-2-oyl)-3,4-dihydro-4,6-dimethylspiro-[quinoline-2,1′-cyclohexane] 6b. This compound was isolated as colorless crystals; mp 97–98°C (from heptane); yield 16%; ν_{max} (KBr) (cm^{-1}) 1651 (C═O); ^1H NMR (400 MHz, $CDCl_3$) δ 0.96 (1H, t, J=12.5 Hz, H_{ax}-3), 1.20–1.95, 2.78, 3.10 (10H, m, $(CH_2)_5$), 1.35 (3H, d, J=6.7 Hz, 4-CH_3), 2.38 (1H, dd, J=2.8, 13.0 Hz, H_{eq}-3), 2.66 (1H, m, H-4), 5.41 (1H, dd, J=2.2, 10.0 Hz, H_X), 6.06 (1H, dd, J=10.0 Hz, H_A), 6.27 (1H, dd, J=17.0 Hz, H_M), 6.76 (1H, d, J=8.0 Hz, H-8), 6.92 (1H, d, J=8.0 Hz, H-7), 6.99 (1H, s, H-5). Mass spectrum (EI): *m/z* (%) 283 ($M^{+\cdot}$, 71), 268 (38), 240 (42), 188 (95), 187 (14), 174 (10), 172 (11), 162 (4), 160 (20), 146 (32), 55 (100). Anal. calcd for $C_{19}H_{25}NO$: C, 80.52; H, 8.89; N, 4.94%. Found: C, 80.33; H, 8.69; N, 4.79%.

4.2.7. 6-Chloro-*N*-(propen-2-oyl)-3,4-dihydro-4-methylspiro[quinoline-2,1′-cyclohexane] 6c. This compound was isolated as colorless crystals; mp 118–120°C (from heptane); yield 24%; ν_{max} (KBr) (cm^{-1}) 1652 (C═O); ^1H NMR (400 MHz, $CDCl_3$) δ 0.93 (1H, t, J= 13.2 Hz, H_{ax}-3), 1.16–1.75, 2.78, 3.05 (10H, m, $(CH_2)_5$), 1.34 (3H, d, J=6.6 Hz, 4-CH_3), 2.41 (1H, dd, J=2.7, 13.2 Hz, H_{eq}-3), 2.65 (1H, m, H-4), 5.42 (1H, dd, J=1.8, 9.9 Hz, H_X), 6.02 (1H, dd, J=9.9 Hz, H_A), 6.30 (1H, dd, J=1.8, 16.5 Hz, H_M), 6.80 (1H, d, J=8.1 Hz, H-8), 7.09 (1H, d, J=8.1 Hz, H-7), 7.15 (1H, s, H-5). Mass spectrum (EI): *m/z* (%) 303 ($M^{+\cdot}$, ^{35}Cl, 28), 288 (16), 260 (15), 208 (35), 207 (22), 194 (6), 192 (6), 182 (4), 180 (11), 166 (12), 55 (100). Anal. calcd for $C_{18}H_{22}ClNO$: C, 71.16; H, 7.30; N, 4.61%. Found: C, 71.11; H, 7.51; N, 4.69%.

4.2.8. *N*-(Propen-2-oyl)-3,4-dihydro-6-fluoro-4-methylspiro[quinoline-2,1′-cyclohexane] 6d. This compound was isolated as colorless crystals; mp 82–84°C (from heptane); yield 23%; ν_{max} (KBr) (cm^{-1}) 1651 (C═O); ^1H NMR (400 MHz, $CDCl_3$) δ 0.87 (1H, dd, J=13.2 Hz, H_{ax}-3), 1.15–1.69, 2.92, 3.05 (10H, m, $(CH_2)_5$), 1.28 (3H, d, J=6.7 Hz, 4-CH_3), 2.33 (1H, dd, J=3.0, 13.0 Hz, H_{eq}-3), 2.62 (1H, m, H-4), 5.38 (1H, dd, J=1.9, 10.1 Hz, H_X), 5.97 (1H, dd, J=10.1 Hz, H_A), 6.21 (1H, dd, J=16.7 Hz, H_M), 6.73 (1H, d, J=8.0 Hz, H-8), 6.76 (1H, t, J=8.3 Hz, H-7), 6.84 (1H, d, J=8.5 Hz, H-5). Mass spectrum (EI): *m/z* (%) 287 ($M^{+\cdot}$, 40), 272 (30), 244 (22), 192 (39), 191 (12), 178 (9),

176 (7), 166 (2), 164 (15), 150 (22), 55 (100). Anal. calcd for $C_{18}H_{22}FNO$: C, 75.23; H, 7.72; N, 4.87%. Found: C, 75.52; H, 7.81; N, 4.75%.

4.3. General procedure for the synthesis of *N*-carbethoxymethyl-3,4-dihydro-4-methylspiro[quinoline-2,1′-cyclohexanes] 7a–e

To stirred mixture of spiranes **3a–e** (1 mmol), KI (0.2 mmol) and Na_2CO_3 (1.5 mmol) in dry acetone (15 ml), a solution (3 ml) of ethyl bromoacetate (1.5 mmol) in acetone was added dropwise for 10 min. After the addition was complete, the solution was heated at reflux for 15–17 h. and monitored by thin layer chromatography. The reaction mixture was then filtered and solvent as well as an excess of ethyl bromoacetate was removed under vacuum. The crude product was fractionated by chromatography on an alumina column using heptane and heptane–ethyl acetate (25:1, 15:1, 10:1) as an eluents to give compounds **7a–e** as maroon viscous oils. The ^1H and ^{13}C NMR data of these compounds are given in Table 2.

4.3.1. *N*-Carbethoxymethyl-3,4-dihydro-4-methylspiro-[quinoline-2,1′-cyclohexane] 7a. This compound was isolated as maroon viscous oil; yield 79%; ν_{max} (film) (cm^{-1}) 1754, 1728 (C=O). Mass spectrum (EI): *m/z* (%) 301 ($M^{+\cdot}$, 43), 286 (51), 272 (5), 258 (100), 245 (7), 228 (96), 214 (3), 206 (2). Anal. calcd for $C_{19}H_{27}NO_2$: C, 75.71; H, 9.03; N, 4.65%. Found: C, 75.58; H, 8.92; N, 4.60%.

4.3.2. *N*-Carbethoxymethyl-3,4-dihydro-4,6-dimethylspiro[quinoline-2,1′-cyclohexane] 7b. This compound was isolated as maroon viscous oil; yield 72%; ν_{max} (film) (cm^{-1}) 1754, 1726 (C=O). Mass spectrum (EI): *m/z* 315 ($M^{+\cdot}$, 55), 300 (54), 286 (6), 272 (100), 259 (8), 242 (95), 228 (3), 220 (2). Anal. calcd for $C_{20}H_{29}NO_2$: C, 76.15; H, 9.27; N, 4.44%. Found: C, 76.07; H, 9.11; N, 4.31%.

4.3.3. 6-Chloro-*N*-carbethoxymethyl-3,4-dihydro-4-methylspiro[quinoline-2,1′-cyclohexane] 7c. This compound was isolated as maroon viscous oil; yield 52%; ν_{max} (film) (cm^{-1}) 1752, 1728 (C=O). Mass spectrum (EI): *m/z* 335 ($M^{+\cdot}$ ^{35}Cl, 45), 320 (52), 306 (4), 292 (100), 279 (9), 262 (92), 248 (4), 240 (3). Anal. calcd for $C_{19}H_{26}ClNO_2$: C, 67.94; H, 7.80; N, 4.17%. Found: C, 67.84; H, 7.70; N, 4.12%.

4.3.4. *N*-Carbethoxymethyl-3,4-dihydro-6-fluoro-4-methylspiro[quinoline-2,1′-cyclohexane] 7d. This compound was isolated as maroon viscous oil; yield 36%; ν_{max} (film) (cm^{-1}) 1752, 1727 (C=O). Mass spectrum (EI): *m/z* 319 ($M^{+\cdot}$, 42), 304 (49), 290 (5), 276 (100), 263 (8), 246 (98), 232 (3), 224 (1). Anal. calcd for $C_{19}H_{26}FNO_2$: C, 71.44; H, 8.20; N, 4.39%. Found: C, 71.60; H, 8.29; N, 4.28%.

4.3.5. 6-Bromo-*N*-carbethoxymethyl-3,4-dihydro-4-methylspiro[quinoline-2,1′-cyclohexane] 7e. This compound was isolated as maroon viscous oil; yield 52%; ν_{max} (film) (cm^{-1}) 1752, 1726 (C=O). Mass spectrum (EI): *m/z* 381 ($M^{+\cdot}$ ^{81}Br, 53), 366 (53), 352 (5), 339 (100), 325 (8), 308 (90), 294 (6), 286 (2). Anal. calcd for $C_{19}H_{26}BrNO_2$: C, 60.00; H, 6.89; N, 3.68%. Found: C, 59.85; H, 6.69; N, 3.53%.

4.4. General procedure for the synthesis of 7-methyl-3-oxo-1,2,6,7-tetrahydrospiro[pyrido(3,2,1-*ij*)quinoline-5,1′-cyclohexanes] 8a–d

A suspension of the *N*-(3-chloropropanoyl) spirodihydroquinolines **5a–d** (1 mmol), $AlCl_3$ (3 mmol) in heptane (5.0 ml) was heated at 100–110°C for 1.5 h. After cooling the reaction mixture was treated with 1N HCl followed by saturated NaOH solution to pH 8 and extracted with CH_2Cl_2 (3×50 ml). The organic layer was dried over anhydrous Na_2SO_4, concentrated in vacuo and the resulting product was fractionated by chromatography on a silica gel column using heptane–ethyl acetate (15:1, 10:1, 5:1) as an eluent to give compounds **8a–d** as crystalline substances. The ^1H and ^{13}C NMR data of these compounds are given in Table 1.

4.4.1. 7-Methyl-3-oxo-1,2,6,7-tetrahydrospiro[pyrido-(3,2,1-*ij*)quinoline-5,1′-cyclohexane] 8a. This compound was isolated as colorless crystals; mp 170–171°C (from heptane); yield 61%; ν_{max} (KBr) (cm^{-1}) 1662 (C=O). Mass spectrum (EI): *m/z* (%) 269 ($M^{+\cdot}$, 35), 254 (13), 240 (3), 226 (25), 212 (25), 210 (2), 200 (5), 198 (7), 186 (18), 184 (8), 174 (100). Anal. calcd for $C_{18}H_{23}NO$: C, 80.26; H, 8.61; N, 5.20%. Found: C, 80.09; H, 8.48; N, 5.14%.

4.4.2. 7,9-Dimethyl-3-oxo-1,2,6,7-tetrahydrospiro[pyrido-(3,2,1-*ij*)quinoline-5,1′-cyclohexane] 8b. This compound was isolated as colorless crystals; mp 145–147°C (from heptane); yield 85%; ν_{max} (KBr) (cm^{-1}) 1662 (C=O). Mass spectrum (EI): *m/z* (%) 283 ($M^{+\cdot}$, 27), 268 (8), 254 (12), 240 (18), 226 (17), 224 (1), 214 (1), 212 (24), 200 (12), 198 (7), 188 (100). Anal. calcd for $C_{19}H_{25}NO$: C, 80.52; H, 8.89; N, 4.94%. Found: C, 80.69; H, 8.78; N, 5.10%.

4.4.3. 9-Chloro-7-methyl-3-oxo-1,2,6,7-tetrahydrospiro-[pyrido(3,2,1-*ij*)quinoline-5,1′-cyclohexane] 8c. This compound was isolated as colorless crystals; mp 95–97°C (from heptane); yield 66%; ν_{max} (KBr) (cm^{-1}) 1670 (C=O). Mass spectrum (EI): *m/z* (%) 303 ($M^{+\cdot}$, ^{35}Cl, 40), 288 (12), 274 (3), 260 (24), 246 (22), 244 (2), 234 (6), 232 (5), 220 (21), 218 (5), 208 (100). Anal. calcd for $C_{18}H_{22}ClNO$: C, 71.16; H, 7.30; N, 4.61%. Found: C, 71.00; H, 7.38; N, 4.56%.

4.4.4. 9-Fluoro-7-methyl-3-oxo-1,2,6,7-tetrahydrospiro-[pyrido(3,2,1-*ij*)quinoline-5,1′-cyclohexane] 8d. This compound was isolated as colorless crystals; mp 135–137°C (from heptane); yield 76%; ν_{max} (KBr) (cm^{-1}) 1661 (C=O). Mass spectrum (EI): *m/z* (%) 287 ($M^{+\cdot}$, 45), 272 (14), 258 (4), 244 (27), 230 (25), 228 (3), 218 (7), 216 (9), 204 (20), 202 (6), 192 (100). Anal. calcd for $C_{18}H_{22}FNO$: C, 75.23; H, 7.72; N, 4.87%. Found: C, 75.16; H, 7.58; N, 4.79%.

4.5. General procedure for the synthesis of 7-methyl-1,2,6,7-tetrahydrospiro[pyrido(3,2,1-*ij*)quinoline-5,1′-cyclohexanes] 10a–e

A suspension of the *N*-carbethoxymethyl spirodihydroquinolines **7a–e** (1.0 g) in PPA (10.0 g) was heated at 140–150°C for 1.5 h. After cooling the solution was treated with saturated NaOH solution to pH 8 and extracted with CH_2Cl_2 (2×50 ml). The organic layer was dried over anhydrous

Na_2SO_4, concentrated in vacuo and the resulting product was fractionated by chromatography on an alumina column using heptane as an eluent to give compounds **10a–e** as viscous oils. The ^1H and ^{13}C NMR data of these compounds are given in Table 2.

4.5.1. 7-Methyl-1,2,6,7-tetrahydrospiro[pyrido(3,2,1-*ij*)-quinoline-5,1′-cyclohexane] 10a. This compound was isolated as red viscous oil; yield 48%; ν_{max} (KBr) (cm^{-1}) 2925, 2857, 1596, 1455. Mass spectrum (EI): *m/z* (%) 255 (TM, 25), 240 (45), 226 (4), 212 (100), 199 (7), 184 (18), 170 (6), 160 (2). Anal. calcd for $C_{18}H_{25}N$: C, 84.65; H, 9.87; N, 5.48%. Found: C, 84.52; H, 9.71; N, 5.44%.

4.5.2. 7,9-Dimethyl-1,2,6,7-tetrahydrospiro[pyrido-(3,2,1-*ij*)quinoline-5,1′-cyclohexane] 10b. This compound was isolated as red viscous oil; yield 50%; ν_{max} (KBr) (cm^{-1}) 2924, 2856, 1615, 1503, 1478, 1460. Mass spectrum (EI): *m/z* (%) 269 ($M^{+\cdot}$, 31), 254 (46), 240 (3), 226 (100), 213 (9), 198 (17), 184 (34), 174 (2). Anal. calcd for $C_{19}H_{27}N$: C, 84.70; H, 10.10; N, 5.20%. Found: C, 84.59; H, 10.20; N, 5.10%.

4.5.3. 9-Chloro-7-methyl-1,2,6,7-tetrahydrospiro[pyrido-(3,2,1-*ij*)quinoline-5,1′-cyclohexane] 10c. This compound was isolated as red viscous oil; yield 57%; ν_{max} (KBr) (cm^{-1}) 2952, 2854, 1588, 1481, 1456. Mass spectrum (EI): *m/z* (%) 289 ($M^{+\cdot}$ ^{35}Cl, 29), 274 (47), 260 (3), 246 (100), 233 (7), 218 (16), 204 (6), 194 (5). Anal. calcd for $C_{18}H_{24}ClN$: C, 74.59; H, 8.35; N, 4.83%. Found: C, 74.49; H, 8.18; N, 4.76%.

4.5.4. 9-Fluoro-7-methyl-1,2,6,7-tetrahydrospiro[pyrido-(3,2,1-*ij*)quinoline-5,1′-cyclohexane] 10d. This compound was isolated as red viscous oil; yield 59%; ν_{max} (KBr) (cm^{-1}) 2926, 2857, 1584, 1455. Mass spectrum (EI): *m/z* (%) 273 ($M^{+\cdot}$, 25), 258 (46), 244 (3), 230 (100), 217 (8), 202 (17), 188 (5), 178 (2). Anal. calcd for $C_{18}H_{24}FN$: C, 79.08; H, 8.85; N, 5.12%. Found: C, 79.00; H, 8.88; N, 5.09%.

4.5.5. 9-Bromo-7-methyl-1,2,6,7-tetrahydrospiro[pyrido-(3,2,1-*ij*)quinoline-5,1′-cyclohexane] 10e. This compound was isolated as red viscous oil; yield 32%; ν_{max} (KBr) (cm^{-1}) 2926, 2858, 1596, 1455. Mass spectrum (EI): *m/z* (%) 335 ($M^{+\cdot}$ ^{81}Br, 33), 320 (49), 306 (3), 290 (100), 279 (7), 264 (13), 250 (3), 240 (5). Anal. calcd for $C_{18}H_{24}BrN$: C, 64.67; H, 7.24; N, 4.19%. Found: C, 64.29; H, 7.03; N, 4.12%.

Acknowledgements

Financial support from the Colciencias is gratefully appreciated (grant No 1102-05-110-97).

References

1. Southorn, J. W.; Buckinghan, J. *Dictionary of Alkaloids*; Chapman & Hall: London, 1989.
2. Stevens, R. V. *The Total Synthesis of Natural Products*; Apsimon, J., Ed.; Wiley: New York, 1977; Vol. 3, pp 489–514.
3. Walter, H. German Offen. DE 4,025,443, 1991; *Chem. Abstr.* **1991**, *114*, 247575r.
4. Zammit, M. D.; Davis, T. P.; Willett, G. D. *Macromolecules* **1997**, *30*, 5655–5659.
5. Malcolm, M. B. Eur. Patent 352,774, 1990; *Chem. Abstr.* **1990**, *113*, 24670w.
6. Pawlowski, G. Eur. Patent Appl. EP 206,270, 1986; *Chem. Abstr.* **1987**, *107*, 7084s.
7. Van Gompel, J.; Schuster, G. B. *J. Org. Chem.* **1987**, *52*, 1465–1468.
8. Kaneko, Y. Jpn. Kokai Tokkyo Koho JP 62,279,335, 1987; *Chem. Abstr.* **1988**, *108*, 213611k.
9. Nagasaka, H.; Ohta, K. Eur. Patent Appl. EP 300,410, 1989; *Chem. Abstr.* **1989**, *110*, 202873n.
10. Kurihara, T.; Matsumoto, S.; Kaino, T.; Kanbara, H.; Kubodera, K. Eur. Patent Appl. EP 326,133, 1989; *Chem. Abstr.* **1990**, *112*, 87901x.
11. Arai, K.; Shimizu, S.; Taguchi, Y.; Yamamoto, Y. *Chem. Pharm. Bull.* **1981**, *29*, 991–999.
12. Bass, R. J.; Koch, R. C.; Richards, H. C.; Thorpe, J. E. *J. Agric. Food Chem.* **1981**, *29*, 576–579.
13. Oxford, A. W.; Bays, D. E.; Cavalla, D. J.; North, P. C. Eur. Patent 403, 261, 1990; *Chem. Abstr.* **1991**, *114*, 228762h.
14. Paris, D.; Cottin, M.; Demonchaux, P.; Augert, G.; Dupassieux, P.; Lenoir, P.; Peck, M. J.; Jasserand, D. *J. Med. Chem.* **1995**, *38*, 669–685.
15. Black, D. St. C.; Kumar, N. *Org. Prep. Proc. Int.* **1991**, *23*, 67.
16. Vejdelek, Z.; Protiva, M. *Collect. Czech. Chem. Commun.* **1990**, *55*, 1290–1296.
17. Malesani, G.; Chiarelotto, G.; Ferlin, M. G.; Bordin, F.; Baccichetti, F.; Carlassare, F.; Vedaldi, D.; Dall'acqua, F. *Farm. Ed. Sci.* **1984**, *39*, 925–934.
18. Valenta, Z.; Deslongchamps, P.; Ellison, R. A.; Wiesner, K. *J. Am. Chem. Soc.* **1964**, *86*, 2533–2534.
19. Katayama, H.; Abe, E.; Kaneko, K. *J. Heterocycl. Chem.* **1982**, *19*, 925–926.
20. Katritzky, A. R.; Rachwal, B.; Rachwal, S.; Abboud, K. A. *J. Org. Chem.* **1996**, *61*, 3117–3126.
21. Katritzky, A. R.; Luo, Zh.; Cui, X.-L. *J. Org. Chem.* **1999**, *64*, 3328–3331.
22. Kuznetsov, V. V.; Palma, A. R.; Prostakov, N. S.; Varlamov, A. V. *Khim. Geterotsikl. Soedin.* **1993**, 1504–1507, *Chem. Abstr.* **1994**, *121*, 231113x.
23. Palma, A. R.; Silva, J.; Stashenko, E.; Martínez, J. R.; Kouznetsov, V. *J. Heterocycl. Chem.* **1999**, *36*, 675–679.
24. Palma, A.; Carrillo, C.; Stashenko, E.; Kouznetsov, V.; Bahsas, A.; Amaro-Luis, J. *Tetrahedron Lett.* **2001**, *42*, 6247–6249.
25. Akita, H.; Naito, T.; Oishi, T. *Chem. Lett.* **1979**, 1365–1368.
26. Nasipuri, D.; Das, G. *J. Chem. Soc., Perkin Trans. 1* **1979**, 2776–2778.
27. Prostakov, N. S.; Kuznetsov, V. V.; Stashenko, E. E. *Khim. Geterotsikl. Soedin.* **1989**, 1514–1519, *Chem. Abstr.* **1990**, *113*, 40424z.
28. Palma, A.; Rozo, W.; Stashenko, E.; Molina, D.; Kouznetsov, V. *J. Heterocycl. Chem.* **1998**, *35*, 183–188.
29. Vargas, L. M.; Rozo, W.; Kouznetsov, V. *Heterocycles* **2000**, *53*, 785–796.
30. Kuznetsov, V. V.; Lantsetov, S. V.; Aliev, A. E.; Varlamov, A. V.; Prostakov, N. S. *Zh. Org. Khim. (Russ.)* **1992**, *28*, 74–78, *Chem. Abstr.* **1992**, *117*, 171194o.

31. Kouznetsov, V.; Palma, A. R.; Salas, S.; Vargas, L. Y.; Zubkov, F.; Varlamov, A.; Martínez, J. R. *J. Heterocycl. Chem.* **1997**, *34*, 1591–1595.
32. Palma, A.; Salas, S.; Kouznetsov, V.; Stashenko, E.; Montenegro, N. G.; Fontela, G. A. *J. Heterocycl. Chem.* **2001**, *38*, 837–842.
33. Ölwegard, M.; McEwen, I.; Thibblin, A.; Ahlberg, P. *J. Am. Chem. Soc.* **1985**, *107*, 7494–7499.
34. Johnston, K. M.; Luker, R. M.; Williams, G. H. *J. Chem. Soc., Perkin Trans. 1* **1972**, 1648–1652.
35. Ogata, Y.; Takagi, K.; Ishino, I. *J. Org. Chem.* **1971**, *36*, 3975–3979.
36. A solution (5.0 ml) of 0.15 g (0.56 mmol) of spirojulolidone **8a** in dry ether was added dropwise with stirring to a suspension of lithium aluminium hydride (1.67 mmol) in 10 ml of ether and the resulting mixture was boiled under reflux for 12 h. The reaction mixture then was decomposed by addition of water (5.0 ml) followed by 15 ml of 10% NaOH solution. The organic layer was separated, dried and concentrated. The residue was purified by alumina column chromatography to obtain 0.1 g (71%) of **10a** as red oil.
37. He, X.; Li, Z.; You, Q. *Synth. Commun.* **2002**, *32*, 709–714.