Pergamon

Tetrahedron Letters 43 (2002) 4707–4709

TETRAHEDRON LETTERS

A simple synthesis of spiro-C_6-annulated hydrocyclopenta[*g*]indole derivatives

Vladimir Kouznetsov,[a,*] Fedor Zubkov,[b] Alirio Palma[a] and Guillermo Restrepo[a]

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

[b]*Department of Organic Chemistry, Russian Peoples Friendship University, Moscow 117923, Russia*

Received 6 March 2002; accepted 16 April 2002

Abstract—A series of new spiro-C_6-annulated hydrogenated cyclopenta[*g*]indoles (**5**) was prepared by applying Madelung method to the appropriate 4-(*N*-acetylamino)-1-spiroindanes (**9**), synthesised via acid-catalysed intramolecular rearrangement of 1-acetyl-3,4-dihydrospiro[quinoline-2,1′-cycloalkanes] (**8**).

The dihydrocyclopenta[*g*]indole subunit is present in several biologically active metabolites isolated from various marine sponges (*Trikentrion flabelliforme*, *Axinell* sp. and *Ectyonanchora flabellata*) including trikentrins A (**1**), trikentrins B (**2**), herbindoles (**3**), and dilemmaones (**4**) (Fig. 1). It was established that these unusual indole derivatives inhibit the growth of the gram-positive bacteria and show high cytotoxic activity.[1–3] Their unique tricyclic structure, which includes a cyclopentane ring annulated to the benzene portion of the indole, has provided a focus for intense synthetic interest.

Several methods to prepare the heterocycles (**1**–**3**) including their enantioselective synthesis have been reported in the literature.[4,5] However, up to now, the hydrocyclopenta[*g*]indoles spiroannulated at C-6 with a cycloalkane ring have not yet been described. As a part of our research efforts towards the spiro heterocycle synthesis and reactivity evaluation,[6] herein we wish to report our results on the preparation of the hydrogenated spirocyclic cyclopenta[*g*]indole derivatives (**5**) and (**6**), analogs of trikentrins (Fig. 1). The main goal of the present research was to devise a practical method for constructing spiro-analogs of trikentrins to study chemical and biological properties of these spiro-heterocyclic systems.

Our approach to the spiro-C_6-annulated hydrocyclopenta[*g*]indoles (**5**,**6**) takes 3,4-dihydrospiro-[quino-

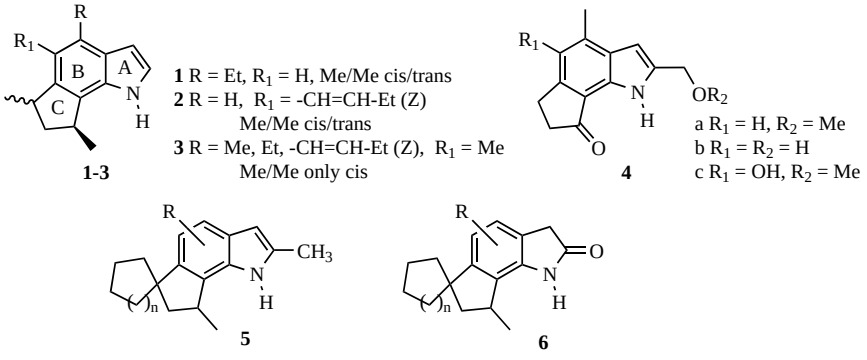
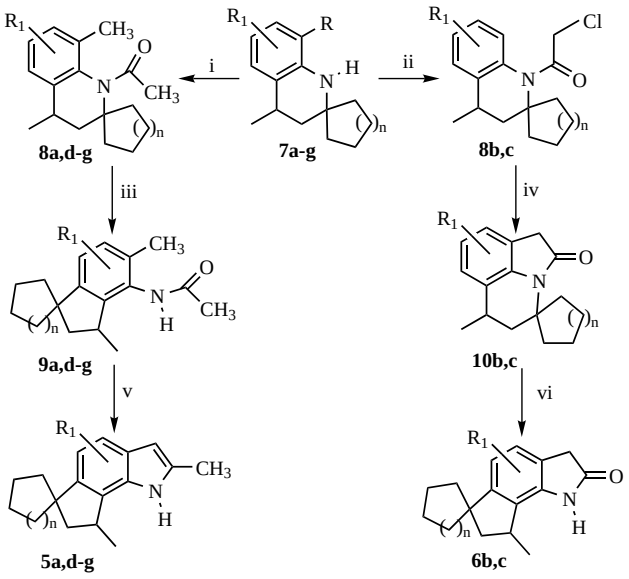


Figure 1. Chemical structures of trikentrins (**1**,**2**), herbindoles (**3**), dilemmaones (**4**) and new spiro-analogs **5** and **6**.

Keywords: hydrocyclopenta[*g*]indoles; aminoindanes; trikentrins; Madelung synthesis.

* Corresponding author. Fax: +57-7-456737; e-mail: kouznet@uis.edu.co

0040-4039/02/$ - see front matter
PII: S0040-4039(02)00847-X



Scheme 1. *Reagents and conditions*: (i) Ac_2O excess, reflux, 2–4 h; (ii) $ClCOCH_2Cl/Et_3N/PhH$, 40°C, 3–6 h; (iii) conc. H_2SO_4, rt, 3–6 h; (iv) $AlCl_3$/heptane, 90–100°C, 1–2 h; (v) $NaNH_2$/DMA, reflux, 1 h; (vi) PPA, 90°C, 3–4 h.

line-2,1′-cycloalkanes] (**7**) and acylated derivatives (**8**) as starting material, and is based on the intramolecular acidic rearrangement of these amides to give the spirocyclic 4-amino-3,5-dimethylindanes (**9**), which in turn serve as suitable precursors in the indole synthesis by Madelung. In addition to this approach, an alternative route to the similar derivatives by the same methodology using chemical properties of 2-oxo-spiro[pyrrolo(3,2,1-*ij*)quinolines] (**10**) as an amide function was realised (Scheme 1).

The required acyl derivatives **8a**–**g** (Table 1) were obtained by acylation with Ac_2O or $ClCH_2COCl/Et_3N$ of respective spiroquinolines **7a**–**g**, previously prepared by three-step procedure from the commercially available cyclic ketones and anilines that includes imine formation, *C*-allylation reaction and acidic cyclisation.[7]

Fascinated with the simple and elegant conversion of 1-acetyl-2,2,4-trimethyl-1,2,3,4-tetrahydroquinoline to 4-*N*-acetylamino-1,1,3-trimethylindane done by Professor Meth-Cohn,[8] we considered that this interesting conversion deserves further investigation and could be employed in our approach.

Thus, the obtained *N*-acetylated spiroquinolines **8a**,**d**–**g** were rearranged by the action of concentrated H_2SO_4 to provide almost quantitatively the 4-*N*-acetylaminoindanes **9a**,**d**–**g**, suitable substrates to effect base-catalysed intramolecular condensation between an aromatic methyl at C-5 and an *ortho* acylamino-substituent. Final spiro-hydrocyclopenta[*g*]indole derivatives **5a**,**d**–**g**[9] were prepared via a modified synthesis of Madelung ($NaNH_2$/DMA (*N*,*N*-dimethylaniline)) in moderate yields (Table 2).

We next turned our attention to the analogous transformation of the 2-oxo-spiro[pyrrolo(3,2,1-*ij*)quinolines] **10b**,**c** that were obtained via the intramolecular Friedel–Crafts alkylation of *N*-α-chloroacetyl spiroderivatives **8b**,**c**.[6b] Further treatment of **10b**,**c** with PPA (80–90°C) produced the similar spiro-hydrocyclopenta[*g*]indolinones **6b**,**c** in excellent yields (Table 2). Thus, the acid-promoted rearrangement of **8a**,**d**–**g** and **10b**,**c** is a key step to provide the spiro-ABC-fragment of trikentrin alkaloids.

In summary, we have developed a new practical synthetic route to spiro analogues of trikentrins. It is based on the intramolecular recyclisation process application of *N*-acetyl-tetrahydroquinolines or pyrroloquinolones that can be used in the synthesis of diverse heterocycles with hydrocyclopenta[*g*]indole backbone. The simplicity of the processes, the easy availability and moderate cost of the starting materials are worthy of mention. Further studies on the possibility of synthesis of diverse hydrocyclopenta[*g*]indole derivatives as well as (acyl)aminoindanes, useful in the preparation of fungicide agents[10] are in progress in our laboratories.

Table 2. Final products in proposed synthesis.

Comp. **5**,**6**	*n*	R_1	Mp (hexane) (°C)	Yield (%)[a]
a	1	H	70–72	30
b	2	H	199–201	89
c	2	5-Cl	208–210	94
d	2	H	101–102	46
e	2	4-CH_3	86–88	43
f	2	5-CH_3	129.5	46
g	3	H	49.5–52.5	32

[a] Yields are given from the respective compounds **9**, **10**.

Table 1. Starting materials **8** in proposed synthesis

Comp. **8**	*n*	R	R_1	Mp (hexane/ethyl acetate) (°C)	Yield (%)
a	1	CH_3	H	56–57	72
b	2	H	H	113–114	68
c	2	H	6-Cl	115–116	57
d	2	CH_3	H	92–93	82
e	2	CH_3	7-CH_3	78–78.5	72
f	2	CH_3	6-CH_3	60–62	75
g	3	CH_3	H	50–51	71

Acknowledgements

The authors are grateful to Alí Bahsas and Juan Amaro-Luis (Laboratorio de RMN, Grupo de Productos Naturales, Departamento de Química, Universidad de Los Andes, Mérida, Venezuela) for the NMR measurements (compounds **6b**,**c**).

References

1. Capon, R. J.; Macleod, J. K.; Scammells, P. J. *Tetrahedron* **1986**, *42*, 6545–6550.
2. Herb, R.; Carroll, A. R.; Yoshida, W. Y.; Scheuer, P. J. *Tetrahedron* **1990**, *46*, 3089–3092.
3. Beukes, D. R.; Davies-Coleman, M. T.; Kelly-Borges, M.; Harper, M. K.; Foulkner, D. J. *J. Nat. Prod.* **1998**, *61*, 699–701.
4. (a) Macleod, J. K.; Monahan, L. C. *Tetrahedron Lett.* **1988**, *29*, 391–392; (b) Muratake, H.; Natsume, M. *Tetrahedron Lett.* **1989**, *30*, 5771–5772; (c) Muratake, H.; Watanabe, M.; Goto, K.; Natsume, M. *Tetrahedron* **1990**, *46*, 4179–4192; (d) Yasukouchi, T.; Kanematsu, K. *Tetrahedron Lett.* **1989**, *30*, 6559–6562; (e) Boger, D. L.; Zhang, M. *J. Am. Chem. Soc.* **1991**, *113*, 4230–4234; (f) Wiedenau, P.; Monse, B.; Blechert, S. *Tetrahedron* **1995**, *51*, 1167–1176; (g) Muratake, H.; Mikawa, A.; Seino, T.; Natsume, M. *Chem. Pharm. Bull.* **1994**, *42*, 848–853.
5. (a) Muratake, H.; Mikawa, A.; Natsume, M. *Tetrahedron Lett.* **1992**, *33*, 4595–4598; (b) Muratake, H.; Seino, T.; Natsume, M. *Tetrahedron Lett.* **1993**, *34*, 4815–4818; (c) Lee, M.; Ikeda, I.; Kawabe, T.; Mori, S.; Kanematsu, K. *J. Org. Chem.* **1996**, *61*, 3406–3416.
6. (a) Vargas, L. Y. M.; Kouznetsov, V. *Heterocycl. Commun.* **1998**, *4*, 341–344; (b) Palma, A. R.; Silva, J.; Stashenko, E.; Martinez, J. R; Kouznetsov, V. *J. Heterocycl. Chem.* **1999**, *36*, 675–679; (c) Vargas, L. Y.; Rozo, W.; Kouznetsov, V. *Heterocycles* **2000**, *53*, 785–796; (d) Varlamov, A.; Kouznetsov, V.; Zubkov, F.; Chernyshev, A.; Alexandrov, G.; Palma, A.; Vargas, L.; Salas, S. *Synthesis* **2001**, 849–854; (e) Palma, A.; Carrillo, C.; Stashenko, E.; Kouznetsov, V.; Bahsas, A.; Amaro-Luis, J. *Tetrahedron Lett.* **2001**, *42*, 6247–6249.
7. (a) Prostakov, N. S.; Kuznetsov, V. V.; Stashenko, E. *Khim. Geterotsikl. Soedin.* **1989**, 1514–1519; *Chem. Abstr.* **1990** [113: 40424z]; (b) Kuznetsov, V. V.; Aliev, A. E.; Palma, A. R.; Varlamov, A. V.; Prostakov, N. S. *Khim. Geterotsikl. Soedin.* **1991**, 947–952; *Chem. Abstr.* **1992** [116: 106.057c].
8. Cliffe, W. H.; Dodman, D.; Meth-Cohn, O. *J. Chem. Soc. C* **1966**, 514–517.
9. Spectral data for compounds (**5**, **6**). Data for compound **5a**: ν_{max} (film)/cm^{-1} 3360 (N-H); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.51 (3H, d, $J=6.8$, 8-CH_3,), 1.75 (1H, dd, $J=7.2$ and 12.4, 7-Hb), 1.96–1.72 (7H, m, spiroalkane), 2.04–2.16 (1H, m, spiroalkane), 2.38 (1H, dd, $J=7.8$ and 12.4, 7-Ha), 2.48 (3H, d, $J=1.0$, 2-CH_3), 3.55 (1H, s, ddq, $J=6.8$, 7.2 and 7.8, 8-H), 6.26 (1H, q, $J=1.0$, 3-H), 6.97 (1H, d, $J=8.1$, 4-H), 7.42 (1H, d, $J=8.1$, 5-H), 7.79 (1H, bs, 1-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.6, 20.5, 24.9, 25.1, 35.9, 40.9, 41.4, 49.9, 54.7, 100.5, 114.3, 118.2, 128.1, 128.2, 132.4, 133.9, 144.0; MS (m/z): 240 (20), 239 (100, M^+), 224 (12), 211 (18), 210 (74), 197 (49), 196 (50), 195 (11), 194 (10), 184 (7), 183 (8), 182 (25), 181 (20), 180 (15), 168 (9), 167 (13), 154 (3), 152 (3), 144 (3), 115 (2), 98 (4), 83 (4), 77 (3), 28 (3). Anal. calcd for $C_{17}H_{21}N$: C, 85.36; H, 8.79; N, 5.86%. Found: C, 85.57; H, 8.90; N, 5.81%. Data for compound **6b**: ν_{max} (KBr)/cm^{-1} 3191 (N-H), 1704 (C=O); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.38–1.88 (10H, m, spiroalkane), 1.37 (3H, d, $J=7.2$, 8-CH_3), 1.69 (1H, dd, $J=7.6$ and 13.0, 7-Hb), 2.38 (1H, dd, $J=8.4$ and 13.0, 7-Ha), 3.33 (1H, ddq, $J=7.2$, 7.6 and 8.4, 8-H), 3.50 (2H, s, 3-H), 6.83 (1H, d, $J=7.9$, 4-H), 7.07 (1H, d, $J=7.9$, 5-H), 9.37 (1H, bs, 1-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.3, 23.0, 23.2, 25.6, 34.8, 36.3, 37.9, 38.9, 44.7, 53.3, 121.8, 123.8, 129.0, 138.8, 142.7, 154.2, 179.5; MS (m/z): 255 ($M^{+\bullet}$, 100), 240 (56), 226 (2), 212 (29), 198 (29), 184 (25), 170 (9). Anal. calcd for $C_{17}H_{21}NO$: C, 80.00; H, 8.24; N, 5.50%. Found: C, 80.18; H, 8.15; N, 5.59%.
10. (a) Tsushina, K.; Osuma, K.; Matsuo, N.; Itaya, N. *Agric. Biol. Chem.* **1989**, *53*, 2529–2530; (b) Kuznetsov, V. V.; Palma, A. R.; Aliev, A. E.; Prostakov, N. S.; Varlamov, A. V. *Khim. Geterotsikl. Soedin.* **1993**, 789–796; *Chem. Abstr.* **1994** [120: 191.496v]; (c) Briner, P. H. Can. Pat. Appl. CA 2,133,942, 1995. *Chem. Abstr.* **1996** [124, 8419t].