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SYNTHESIS AND SEPARATION OF NEW DIBENZ[b,d]AZONINE ATROPISOMERS

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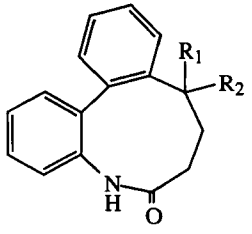
Abstract: A synthesis of the dibenz[b,d]azonine atropisomers (**14**) from 2-phenylbenzoic acid is described. This heterocycle belongs to a new series of biaryl compounds with potential antitubulin activity.

As part of our research on the discovery of new bioactive compounds[1], we were interested in the synthesis of dibenzo[b,d]azonine derivatives **1** which are structurally related to the antitubulin rhazinilam **2** [2-3] and phenylpyrroles **3**. [4-5]



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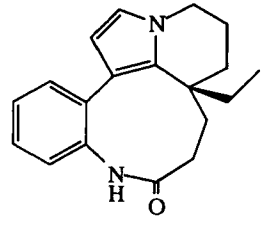

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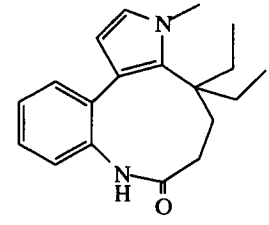

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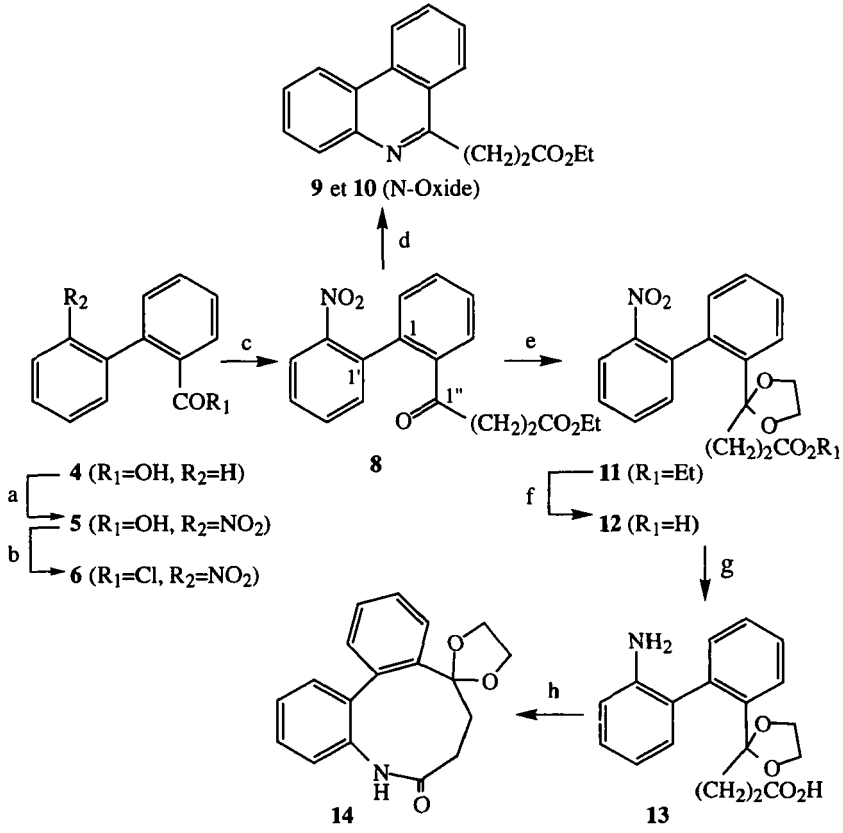
The synthesis of dibenzazonine lactams such as **1** has never been reported in the literature. So we decided to use the most direct approach to prepare the first compound of this new series (Scheme 1). Electrophilic nitration[6] of commercial 2-biphenylcarboxylic acid **4** led to 2-(2'-nitrophenyl)benzoic acid **5** which gave quantitatively the acid chloride **6** after treatment with thionyl chloride. The conversion of **6** to the γ-keto ester **8** was achieved using the palladium catalyzed coupling with 2-carboethoxyethylzinc iodide **7** generated by the treatment of ethyl 3-iodopropionate with Zn-Cu couple[7].

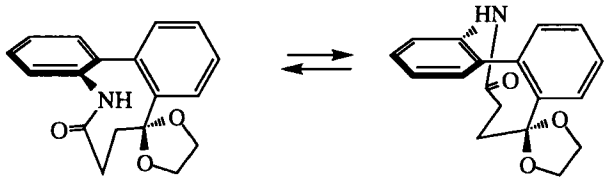


a) HNO_3 (45%), b) $SOCl_2$ (100%), c) $I(CH_2)_2CO_2Et$ **7**, Zn-Cu, $Pd(PPh_3)_4$ (85%), d) Pd/C, H_2, EtOH, (**9** (8%), **10** (14%)), e) $HO(CH_2)_2OH$, TMSCl, CH_2Cl_2-DME (20%), f) NaOH, MeOH (100%) g) H_2, PtO_2 (97%), h) EDCI, HOBT, CH_2Cl_2, high dilution (72%).

Scheme 1

To avoid the formation of phenanthridine derivatives **9** and **10** occurring after direct hydrogenation of **8**, the keto group was protected with ethylene glycol [8] to give the ethyl ester **11**[9]. Hydrolysis of **11** led to acid **12** which was hydrogenated to give the amino-acid **13**. The most effective method for the intramolecular cyclization was to treat **13** with EDCI as coupling agent, under high dilution conditions in methylene chloride. Thus, the racemic tricyclic biphenyl lactam **14** was obtained with a yield of 72%.

Taking into account the axial chirality of the biphenyl system in this series (scheme 2), we separated the atropisomers using a chiral column. Then we performed enantiomerization experiments to determine the energy barrier of the atropisomers **14**. The analysis of the thermal enantiomerization performed in 1-pentanol led to an energy barrier of 28.6 Kcal mol^{-1} at 110°C ($t_{1/2}^{110°C}$ = 27.8 min for atropisomer (-) **14**).[10]



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Scheme 2

In conclusion, we have prepared the first dibenzo[b,d]azonine atropisomers belonging to a new series of potential antitubulin agents. A detailed account of structure-activity relationships in this series will be published in due course.

Experimental

IR spectra were recorded on a Nicolet 250FT-IR apparatus. ^{1}H and ^{13}C NMR were recorded with Brucker AC 200, AC 250 or AM 300 instruments. Chemical shifts are given as δ values and are related to TMS as internal standard. Mass spectra were obtained on an AEI MS9 spectrometer. Elemental analyses were performed at the ICSN, CNRS, Gif-sur-Yvette, France. Column chromatography was performed on Kieselgel 60 (Merk). HPLC analysis were carried out on a Waters apparatus using a Chiracel OD column (25 x 0.46 cm).

3-[2-(2'-Nitrobiphenyl-2-yl)-oxo-2-yl]propionic acid ethyl ester 8

Into an argon purged flask containing 150 mg (2.3 mmol) of Zn-Cu couple was

added a solution of ethyl 3-iodopropionate (330 mg, 1.5 mmol) in dry benzene (3 ml) containing DMA (0.2 ml). The mixture was stirred at room temperature for 1 h., then at 60°C for 3 h.. To this mixture was added successively a suspension of tetrakis(triphenylphosphine)palladium(0) (46mg, 0.04 mmol) in dry benzene (0.5 ml) and a solution of 2'-nitrobiphenyl acid chloride (250 mg, 1 mmol) in dry benzene (0.5 ml). After 30 min., ethyl acetate was added, and the reaction mixture was successively washed with HCl (1N), $NaHCO_3$ and aqueous NaCl. The organic solution was dried over magnesium sulfate, filtered and evaporated. The desired compound **8** was obtained after chromatography using heptane/ethyl acetate (70/30) as eluant (85%;); ir ($CHCl_3$) υ cm^{-1}: 1735, 1690, 1560, 1350; 1H nmr (250 MHz, $CDCl_3$): δ 8.07 (dd, J=8 and 1 Hz, 1H, Ph), 7.91 (dd, J=8 and 2 Hz, 1H, Ph), 7.63 (bt, J=8 Hz, 1H, Ph), 7.54 (bt, J=8 Hz, 1H, Ph), 7.52 (m, 2H, Ph), 7.35 (dd, J=8 and 1 Hz, 1H, Ph), 7.22 (dd, J=8 and 2 Hz, 1H, Ph), 4.11 (q, J=8 Hz, 2H, $CO_2C\underline{H}_2CH_3$), 3.14 and 2.54 (2m, 4H, CH_2), 1.21 (t, J=8 Hz, 3H, $CO_2CH_2C\underline{H}_3$). ^{13}C nmr (75 MHz, $CDCl_3$): δ 200 (CO), 173 (CO_2Et), 148 ($C_{2'}$), 139 ($C_{1'}$), 137 (C_1, C_2), 133-124 (Ph), 61 ($CO_2\underline{C}H_2CH_3$), 35-28 (CH_2), 14 ($CO_2CH_2\underline{C}H_3$); (IE) m/z =297 ($M^{+\cdot}$ - NO), 282 ($M^{+\cdot}$ - C_2H_5), 281 ($M^{+\cdot}$ - NO_2), 254 ($M^{+\cdot}$ - $CO_2C_2H_5$), 226 ($M^{+\cdot}$ - $CH_2CH_2CO_2Et$), 180 ($M^{+\cdot}$ - NO_2 - $CH_2CH_2CO_2Et$); *Anal.* Calcd. for $C_{18}H_{17}NO_5$: C, 66.05; H, 5.24; N, 4.28; O, 24.44; found: C, 65.76; H, 5.43; N, 4.16; O, 24.58.

3-Phenanthridin-6-yl-propionic acid ethyl ester 9 and its N-Oxide 10

Compound **8** (100 mg, 0.3 mmol) was dissolved in EtOH (2 ml) and hydrogenated over 10°% Pd/C for 3 h. The catalyst was removed by filtration, and the solution was concentrated by evaporation. Purification by thick layer chromatography (heptane / ethyl acetate (60 / 40)) led to compounds **9** (8%) and **10** (14%). **9**: ^1H nmr (250 MHz, $CDCl_3$): δ 8.65 (d, J=8 Hz, 1H, Ph), 8.54 (dd, J=8 and 2 Hz, 1H, Ph), 8.29 (d, J=8 Hz, 1H, Ph), 8.09 (dd, J=8 and 2 Hz, 1H, Ph), 7.85 (tl, J=8 Hz, 1H, Ph), 7.69 (m, 3H, Ph), 4.20 (q, J=7 Hz, 2H, $CO_2C\underline{H}_2CH_3$), 3.71 (t, J=7 Hz, 2H, $H_{2''}$), 3.09 (t, J=7 Hz, 2H, $H_{3''}$), 1.29 (t, J=7 Hz, 3H, $CO_2CH_2C\underline{H}_3$). (IE) m/z = 279 ($M^{+\cdot}$), 250, 234, 206, 178, 152. **10** ^1H nmr (250 MHz, $CDCl_3$): δ 8.94 (dd, J=8 and 2 Hz, 1H, Ph), 8.58 (m, 2H, Ph), 8.14 (m, 1H, Ph), 7.75 (m, 4H, Ph), 4.12 (q, J=7 Hz, 2H, $CO_2C\underline{H}_2CH_3$), 3.85 (t, J=7 Hz, 2H, $H_{2''}$), 2.95 (t, J=7 Hz, 2H, $H_{3''}$), 1.19 (t, J=7 Hz, 3H, $CO_2CH_2C\underline{H}_3$). (IE) m/z = 295 ($M^{+\cdot}$), 279, 250, 234, 206, 178.

3-[2-(2'-Nitrobiphenyl-2-yl)-[1,3]dioxolan-2-yl]propionic acid ethyl ester 11

To a solution of **8** (150 mg, 0.44 mmol) in dry ethylene glycol (2 ml) and methylene chloride (1.5 ml) was added under argon 580 µl of $(CH_3)_3SiCl$ (4.6 mmol). The reaction mixture was stirred for 5 h. at room temperature. The mixture was made basic with saturated $NaHCO_3$ and extracted with CH_2Cl_2. The organic layer was washed with brine and concentrated. The crude extract was purified by column chromatography using heptane / ethyl acetate (60 / 40) as eluant to give esters **11** (20%)[9]; ir ($CHCl_3$) ν 1730, 1530, 1360 cm^{-1}; ^1H nmr (250 MHz, $CDCl_3$): δ 8.07 (dd, J=8 and 1Hz, 1H, Ph), 7.61 (m 2H, Ph), 7.57 (bt, J=8 Hz, 1H, Ph), 7.37 (m, 3H, Ph), 7.15 (dd, 1H, Ph), 4.01 (q, J=8 Hz, 2H, $CO_2C\underline{H}_2CH_3$), 3.89-3.55 (m, 4H, $OC\underline{H}_2C\underline{H}_2O$), 2.28 and 1.90 (2m, 4H, CH_2), 1.18 (t, J=8 Hz, 3H, $CO_2CH_2C\underline{H}_3$); ^{13}C nmr (75 MHz, $CDCl_3$): δ 174 (CO_2Et), 149 ($C_{2'}$), 139 ($C_{1'}$), 137 (C_2, $C_{1'}$), 133-124 (Ph), 110 ($C_{1''}$), 66-65($O\underline{C}H_2\underline{C}H_2O$), 61 ($CO_2\underline{C}H_2$- CH_3), 36-29 (CH_2), 15 (CO_2-$CH_2\underline{C}H_3$); (IE) m/z = 342 ($M^{+\cdot}$ -C_2H_5), 327, 326, 298, 281, 270; *Anal.* Calcd. for $C_{20}H_{21}NO_6$: C, 64.68; H, 5.70; N, 3.77; O, 25.85; found: C, 64.66; H, 5.93; N, 3.76; O, 25.55.

3-[2-(2'-Nitrobiphenyl-2-yl)-[1,3]dioxolan-2-yl]propionic acid 12

The ester **11** (100 mg) was hydrolyzed at 60°C with 50% NaOH in MeOH. After 2 h., the reaction mixture was cooled, acidified with HCl 1N to pH 3 and extracted with ethyl acetate. The organic layer was dried over magnesium sulfate, filtrated and evaporated to give the corresponding acid **12** in quantitative yield. ir ($CHCl_3$) ν 1700, 1530, 1360 cm^{-1}; ^1H nmr (250 MHz, $CDCl_3$): δ 8.09 (dd, J=8 and 2 Hz, 1H, Ph), 7.62 (m, 2H, Ph), 7.51 (td, J=8 and 2 Hz, 1H, Ph), 7,39 (m, 2H, Ph), 7;31 (dd, J=8 and 2 Hz, 1H, Ph), 7.17 (m, 1H, Ph), 3.92-3.58 (m, 4H, $OC\underline{H}_2C\underline{H}_2O$), 2.27 (m, 2H, CH_2), 1.94 (t, J=7 Hz, 2H, CH_2); ^{13}C nmr (62,5 MHz): δ 177 (CO_2H), 152-138 (C_1, C_2, $C_{1'}$, $C_{2'}$), 134-125 (Ph), 110 ($C_{1''}$), 66-65 ($O\underline{C}H_2\underline{C}H_2O$), 36 ($CH_2$), 30 ($CH_2$); (IE) m/z 326 ($M^{+\cdot}$ - OH), 270 ($M^{+\cdot}$ - CH_2CH_2COH); *Anal.* Calcd. for $C_{18}H_{17}NO_6$: C, 62.97, H, 4.99, N, 4.08, O, 27.96; found: C, 63.26, H, 5.17, N, 4.04, O, 27.52.

3-[2-(2'-Aminobiphenyl-2-yl)-[1,3]dioxolan-2-yl]propionic acid 13

To a solution of **12** (80 mg, 0.26 mmol) in ethanol (5 ml) was added PtO_2 (8 mg). The solution was hydrogenated for 14 h., then filtered over Celite. Evaporation of the solvent led to a solid fraction which was purified by column chromatography

using heptane / ethyl acetate (70/30) as eluant to give **13** (97%); ir ($CHCl_3$) ν 3450, 1730, 1630 cm^{-1}; ^1H nmr (300 MHz, $CDCl_3$): δ 7.97 (t, J= 6 Hz, 1H, Ph), 7.62 (m, 2H, Ph), 7.42 (m, 2H, Ph), 6.90 (d, J=7 Hz, 1H, Ph), 6.75 (m, 2H, Ph), 3.87-3.69 (m, 4H, OCH_2CH_2O), 3.70 (bs, 2H, NH_2), 2.15 (t, J=7 Hz, 2H, CH_2), 2.05 (t, J=7 Hz, 2H, CH_2); ^{13}C nmr (75 MHz, $CDCl_3$): δ 180 (CO_2H), 160 ($C_{2'}$), 143 (C_1), 140 (C_2), 137 ($C_{1'}$), 132-114 (Ph), 109 ($C_{1''}$), 65-64 (OCH_2CH_2O), 34 (CH_2), 29 (CH_2); (IE) m/z = 313 ($M^{+\cdot}$), 252, 240.

9-[1,3-Dioxolan-2-yl]-5,7,8,9-tetrahydro-5-azadibenzo[a,c]cyclononene-6-one 14

Into an argon purged flask containing 307 mg (1.6 mmol) of EDCI and 216 mg (1.6 mmol) of HOBT in 1.5 l of anhydrous CH_2Cl_2, were added slowly 500 mg (1.6 mmol) of compound **13** and 223 µl (1.6 mmol) of NEt_3 in 50 ml of CH_2Cl_2 at 0°C. At the end of the addition the mixture was stirred 36 h. at room temperature. After evaporation of CH_2Cl_2, the mixture was made slightly acid and extracted with ethyl acetate. The organic solution was washed with Na_2CO_3 and brine, then dried over Na_2SO_4. The desired compound **14** was obtained after chromatography using heptane/ethyl acetate (70/30) as eluant (72%); ir ($CHCl_3$) ν 3380, 1670cm^{-1}; ^1H nmr (300 MHz, $CDCl_3$): δ 7.54 (dd, J=8 and 1 Hz, 1H, Ph), 7.20 (m, 6H, Ph), 6.78 (dd, J=8 and 1 Hz, 1H, Ph), 3.59-3.80 (m, 4H,OCH_2CH_2O), 2.15 and 2.40 (2m, 4H, CH_2); ^{13}C nmr (75MHz, $CDCl_3$) δ 176 (CO), 135-145 (C_1, C_2, $C_{1'}$ and $C_{2'}$), 128-130 (Ph), 109 ($C_{1''}$), 63 (OCH_2CH_2O), 29 and 38 (CH_2); (IE) m/z = 295 ($M^{+\cdot}$); *Anal.* Calcd. for $C_{18}H_{17}NO_3$: C, 73.20; H, 5.80; N, 4.74; O, 16.25; found: C, 73.55, H, 5.83; N, 4.63; O, 15.99.

Atropisomeric biphenyls **14** were separated at room temperature by HPLC on a Chiracel OD column using hexane-ethanol (95-5) as solvent at 0.5 ml/mn. Retention time of the enantiomers were 45 min for (+) **14** (92% ee) and 48 min for (-) **14** (100% ee) ($[\alpha_D^{22°C}]$= -200 (c= 1.63, EtOH), cd ($CHCl_3$) λ max (Δε) 225 (+0.78), 235 (-1.3).

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References and notes

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INSA, Mont Saint Aignan). The purpose of this program is the synthesis of new biaryl compounds of potential biological interest.

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9- The protection with ethylene glycol and trimethylsilyl chloride led also to a transesterification reaction leading to 2-hydroxyethyl and 2-chloroethyl esters with a yield of 28 and 13%. These two esters are hydrolyzed in the same conditions that ethyl ester **11** to give quantitatively the nitro-acid **12.**

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