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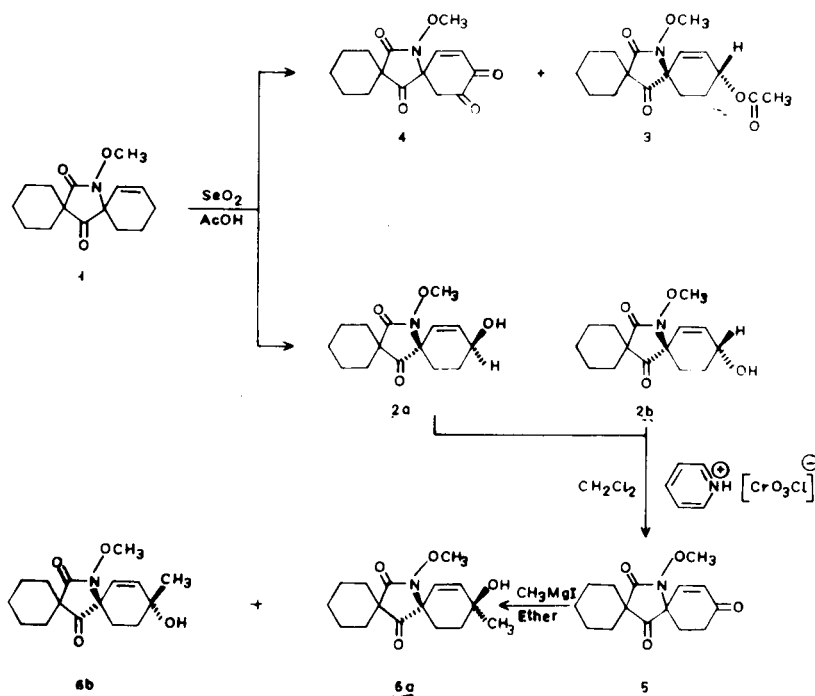
A facile synthesis, which permits regioselective incorporation of hydroxy and/or methyl substituents at position 11 of 14-methoxy-14-azadispiro[5.1.5.2]pentadec-9-ene-7,15-dione, has been described.

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The need for the synthesis of 11-hydroxy and 11-hydroxy-11-methyl-14-methoxy-14-azadispiro[5.1.5.2]pentadec-9-ene-7,15-diones **2** and **6** arose during the course of our investigation on selective  $\beta_1$ -blockers. However, this type of disymmetrical azadispiro compounds, in principle, cannot be synthesized by any of the methods reported earlier [2,3]. This prompted us to develop a facile synthesis of the title compounds. The interesting feature of this synthesis relates to regioselective incorporation of substituents in the molecular architecture of the desired spiro compounds. The details are presented here.

Oxidation of 14-methoxy-14-azadispiro[5.1.5.2]pentadec-9-ene-7,15-dione (**1**) with selenium dioxide in acetic acid yielded a stereoisomeric mixture of **2** (**2a** and **2b**) along with **3** and **4** (Figure 1). These were separated by column chromatography over silica gel. The stereochemical assignment of **2a** and **2b** was made on the basis of  $\text{Eu}(\text{fod})_3$  induced downfield shift of the methoxy signal. Compound **2a** with a pseudoaxial hydroxy group exhibited a predominant downfield shift of the methoxy signal while

the one (**2b**) with a pseudoequatorial hydroxy group exhibited predominant downfield shift of C-10H but not the methoxy signal. The stereochemical assignment of **3** was ascertained by acetylating **2b** and the acetyl derivative so obtained was found to be identical with **3**. This indicated that the acetoxy group in **3** is pseudoequatorial. The structure of **4** was confirmed by various spectroscopic and analytical data. The selenium dioxide oxidation of **1** in dry methanol exclusively gave **4** while in aqueous methanol a mixture of **4** and **2** was obtained. Similarly in aqueous dioxane the oxidation products of **1** were identified as **4** and **2**. Pyridinium chlorochromate oxidation of the mixture of **2a** and **2b** gave **5**. Reaction of this enone with methyl magnesium iodide gave a stereoisomeric mixture of **6** (**6a** and **6b**) which were separated by column chromatography over silica gel. The stereochemical assignment of these two compounds, **6a** and **6b** was made on the basis of  $\text{Eu}(\text{fod})_3$  induced shift of diagnostic pmr signals, similar to the one reported for **2a** and **2b**. The 1,2-addition of methyl magnesium iodide is not unusual since hindered enones are known to give 1,2-addition products [4].



## EXPERIMENTAL

Melting points were determined on an electrically heated block and are uncorrected. The ir spectra were recorded on a Perkin-Elmer 157 grating instrument. The  $^1\text{H}$  nmr spectra were recorded on a Perkin Elmer R-32 spectrometer using tetramethylsilane as internal reference. Europium(III) tris-1,1,1,2,2,3,3-heptafluoro-7,7-dimethyl-4,5-octanedione,  $[\text{Eu}(\text{fod})_3]$  was used as the shift reagent. Mass spectra were recorded on Jeol-JMS-D300.

14-Methoxy-14-azadispiro[5.1.5.2]pentadec-9-ene-7,15-dione (**1**).

This compound was prepared by the method reported in literature [5].

Reaction of **1** with Selenium Dioxide in Acetic Acid. Isolation of Compounds **2-4**.

A mixture of **1** (7.2 g, 0.03 mole) and selenium dioxide (0.66 g, 0.06 mole) in acetic acid (20 ml) was heated under stirring for 0.5 hour. The reaction mixture was filtered and the filtrate concentrated *in vacuo* to furnish an oil which was purified by column chromatography over silica gel. Elution of the column with petroleum ether gave **4** which was crystallized from petroleum ether to give **4** as crystalline solid (15%), mp 84-85°;  $^1\text{H}$  nmr (deuteriochloroform):  $\delta$  1.75 (m, 12H), 3.80 (s, 3H), 5.35 (d, 1H,  $J = 9.9$  Hz), 6.22 (d, 1H,  $J = 9.0$  Hz); ir (potassium bromide): 1750, 1690 and 1660  $\text{cm}^{-1}$ ; ms: 291 ( $\text{M}^+$ ).

*Anal.* Calcd. for  $\text{C}_{15}\text{H}_{17}\text{NO}_5$ : C, 61.85; H, 5.84; N, 4.81. Found: C, 61.72; H, 5.73; N, 4.84.

Further elution of the column with petroleum ether:chloroform mixture (9:1) gave **3** which was crystallized from petroleum benzene giving fine needles (15%), mp 94-96°;  $^1\text{H}$  nmr (deuteriochloroform):  $\delta$  1.60 (m, 14H), 2.04 (s, 3H), 3.89 (s, 3H), 5.25 (m, 1H), 5.56 (d, 1H,  $J = 9.0$  Hz), 6.21 (dd, 1H,  $J = 3.60$  and 10.80 Hz); ir (potassium bromide): 1758, 1720 and 1700  $\text{cm}^{-1}$ ; ms: 321 ( $\text{M}^+$ ).

*Anal.* Calcd. for  $\text{C}_{17}\text{H}_{23}\text{NO}_5 \cdot \frac{1}{2}\text{H}_2\text{O}$ : C, 61.81; H, 7.27; N, 4.24. Found: C, 61.55; H, 6.97; N, 4.20.

The next compound was obtained by eluting the column with a petroleum ether:chloroform mixture (1:1) was **2a** (20%) which was crystallized from petroleum benzene, mp 108°;  $^1\text{H}$  nmr (deuteriochloroform):  $\delta$  1.80 (m, 14H), 3.88 (s, 3H), 4.24 (m, 1H), 5.35 (d, 1H,  $J = 9.9$  Hz), 6.07 (dd, 1H,  $J = 1.80$  and 10.80 Hz), 7.85 (br s, 1H); ir (potassium bromide): 3400, 1750 and 1690  $\text{cm}^{-1}$ ; ms: 279 ( $\text{M}^+$ ).

*Anal.* Calcd. for  $\text{C}_{15}\text{H}_{21}\text{NO}_4 \cdot \text{H}_2\text{O}$ : C, 60.60; H, 7.74; N, 4.71. Found: C, 60.70; H, 7.78; N, 4.80.

Final elution of the column with chloroform gave **2b** which was crystallized from methanol as fine needles (40%), mp 130-132°;  $^1\text{H}$  nmr (deuteriochloroform):  $\delta$  1.85 (m, 14H), 3.88 (s, 3H), 4.21 (m, 1H), 5.41 (d, 1H,  $J = 9.90$  Hz), 6.21 (dd, 1H,  $J = 4.50$  and 9.00 Hz), 7.80 (br s, 1H); ir (potassium bromide): 3400, 1760 and 1700  $\text{cm}^{-1}$ ; ms: 279 ( $\text{M}^+$ ).

*Anal.* Calcd. for  $\text{C}_{15}\text{H}_{21}\text{NO}_4$ : C, 64.51; H, 7.58; N, 5.01. Found: C, 64.50; H, 7.78; N, 5.00.

14-Methoxy-14-azadispiro[5.1.5.2]pentadec-9-ene-7,11,15-trione (**5**).

To a well stirred solution of **2** (2.7 g, 0.01 mole) in dry dichloromethane (40 ml) was added pyridinium chlorochromate (4.4 g, 0.020 mole) and the reaction mixture was stirred at room temperature (30°) for 0.5 hour. It was then extracted with dry diethyl ether (3  $\times$  50 ml) and the ethereal extract after concentration was passed through a band of florisil using chloroform:ethyl acetate mixture (4:1) as eluant. Removal of the solvent yielded a gum which on trituration with petroleum benzene furnished **5** as a crystalline solid (95%), mp 105-106°;  $^1\text{H}$  nmr (deuteriochloroform):  $\delta$  1.75 (m, 14H), 3.92 (s, 3H), 6.21 (d, 1H,  $J = 11.70$  Hz), 6.50 (d, 1H,  $J = 10.80$  Hz); ir (potassium bromide): 1760, 1715 and 1690  $\text{cm}^{-1}$ ; ms: 277 ( $\text{M}^+$ ).

*Anal.* Calcd. for  $\text{C}_{15}\text{H}_{19}\text{NO}_4$ : C, 64.98; H, 6.85; N, 5.05. Found: C, 64.90; H, 6.80; N, 4.77.

11-Hydroxy-11-methyl-14-methoxy-14-azadispiro[5.1.5.2]pentadec-9-ene-7,15-dione (**6a** and **6b**).

To a well stirred suspension of methyl magnesium iodide (prepared from 0.006 mole of magnesium and 0.006 mole of methyl iodide in ether) in dry diethyl ether (50 ml) was added a solution of **5** (0.82 g, 0.003 mole) in tetrahydrofuran (30 ml) and the suspension was stirred at room temperature (35°) for 0.5 hour. To the reaction mixture was added hydrochloric acid (10%, 40 ml) and extracted with ethyl acetate (2  $\times$  250 ml). The organic layer was successively washed with water, dried over anhydrous sodium sulphate and concentrated to yield an oil which was purified by column chromatography over silica gel. Elution of the column with petroleum ether:chloroform mixture (4:1) gave **6a** (10%) as an oil;  $^1\text{H}$  nmr (deuteriochloroform): 1.33 (s, 3H), 1.95 (m, 14H), 3.85 (s, 3H), 5.47 (d, 1H,  $J = 9.90$  Hz), 6.10 (d, 1H,  $J = 9.90$  Hz); ir (Neat): 3380, 1750 and 1700  $\text{cm}^{-1}$ ; ms: 293 ( $\text{M}^+$ ).

*Anal.* Calcd. for  $\text{C}_{16}\text{H}_{23}\text{NO}_4$ : C, 65.52; H, 7.84; N, 4.77. Found: C, 65.40; H, 7.70; N, 4.70.

Further elution of the column with petroleum ether:chloroform mixture (1:1) gave **6b**, which was crystallized from petroleum ether (45%), mp 136-138°;  $^1\text{H}$  nmr (deuteriochloroform):  $\delta$  1.31 (s, 3H), 1.90 (m, 14H), 3.87 (s, 3H), 5.32 (d, 1H,  $J = 9.90$  Hz), 6.02 (d, 1H,  $J = 10.8$  Hz); ir (potassium bromide): 3400, 1758 and 1690  $\text{cm}^{-1}$ ; ms: 293 ( $\text{M}^+$ ).

*Anal.* Calcd. for  $\text{C}_{16}\text{H}_{23}\text{NO}_4$ : C, 65.52; H, 7.84; N, 4.77. Found: C, 65.70; H, 7.80; N, 4.85.

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