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SYNTHESIS OF DERIVATIVES STRUCTURALLY RELATED TO GLAZIOVINE

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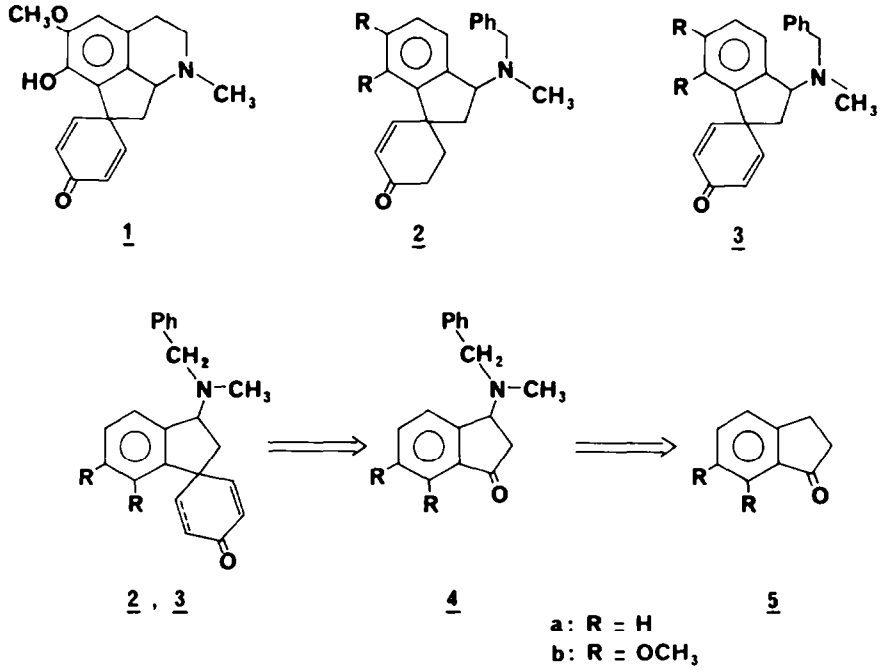
Abstract—Three compounds, **2a**, **2b**, and **2c** have been synthesized by an analogy with glaziovine **1** which has been claimed to have anxiolytic properties similar to diazepam. The intermediates indanones **5** have been obtained according to conventional (for **5a**) or less conventional procedure (**5b**) and then converted to the corresponding indanones **11**. Michael addition of methylbenzylamine followed by a one-carbon homologation of the ketone gave an aldehyde suitable for Robinson annulation leading to the spiro compounds **2**. DDQ oxidation gave **3**. No anxiolytic activity was found from the pharmacological data.

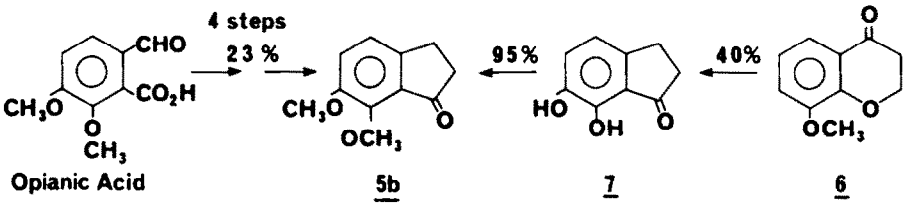
In a search for new anxiolytic drugs, three compounds (**2a**, **2b** and **3**) structurally related to members of the proaporphine alkaloids family have been synthesized. None of the compounds displays any biological activity. Proaporphine alkaloids have been found in members of the plant families Annonaceae and Liliaceae[1] and, for those of them containing a dienone system, a pharmacological activity has been claimed.[2-4] The most exciting compound of this class is certainly glaziovine **1**, an alkaloid from *Ocotea glaziovii*, which displays a promising potential as a tranquilizer. In a double-blind trial vs diazepam in patients with psychoneurotic or psychotic disorders, glaziovine appears to have anxiolytic properties similar to diazepam without causing any drowsiness.[5]

These results, together with our interest in finding a new anxiolytic drug, prompted us to design and synthesize analogs of glaziovine **1**. Our first target molecules were of the types **2** and **3** in which most of the structural features of **1** are retained.

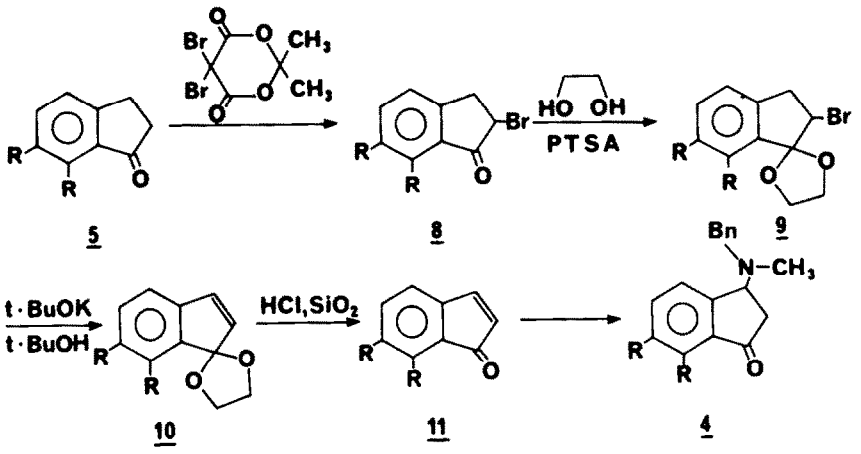
A retro-synthetic scheme for the synthesis of derivatives **2** (Scheme 1) led us to start the synthesis with indanones **5**. Both indanones **5a** and **5b** were known compounds but if **5a** is commercially available, **5b** had to be prepared. We first used a 4 steps sequence as described in the literature which, starting with opianic acid, gave us **5b** in a 23% overall yield.[6] We then developed a more efficient synthesis starting with the methoxy - 8 - chromanone **6**,[7] which, upon fusion with a melt of anhydrous $AlCl_3$ and NaCl,[8] rearranged to the dihydroxyindanone **7**[9] (Scheme 2). Methylation of **7** afforded **5b** in a 38% overall yield.



Scheme 1.



Scheme 2.

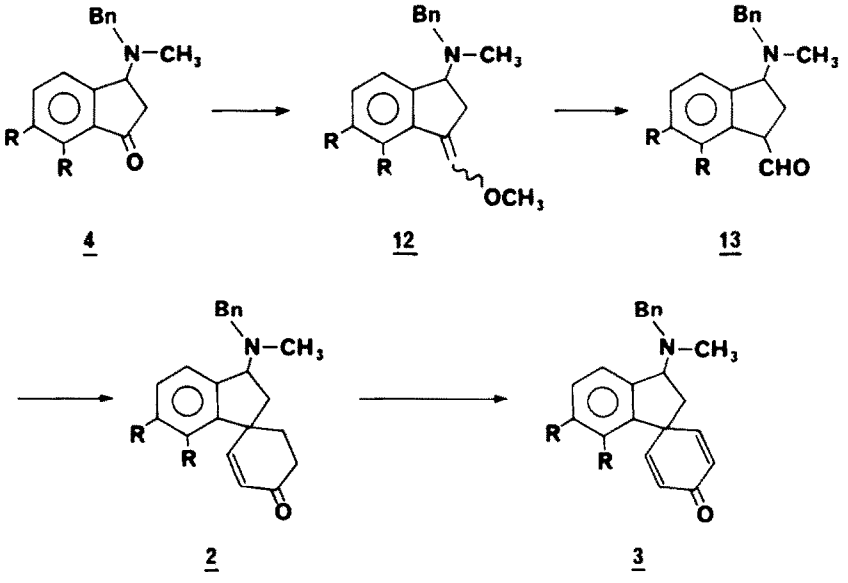


Scheme 3.

At the first glance, transformation of indanone **5** into indenones seemed to be a trivial problem but all the short and direct methods we tried failed.[10] Finally the 4 steps sequence depicted in Scheme 3 turned out to be the most efficient.

The bromoketones **8a** and **8b** obtained by bromination[11] were dehydrobrominated as their dioxolanes. Removal of the protecting group[12] afforded the indenones **11**.[13] Michael additions of the methyl-benzylamine on **11** gave **4** in quantitiative yields.

At the time we started this work a few spiroannulations in the proaporphine alkaloids family had been described, all of them involving homologation of the ketone to the corresponding aldehyde followed by a Robinson annulation.[14] The major drawback of this sequence was the poor overall yield. The very elegant



Scheme 4.

Table 1. Complete analytical data for new stable compounds.

			C	H	N	Cl
4b	$C_{19}H_{22}ClNO_3$	Calc	65.61	6.38	4.03	
		Found	65.23	6.22	4.08	
			C	H	N	Cl
2a	$C_{22}H_{24}ClNO$	Calc :	74.67	6.83	3.96	10.02
		Found	74.24	6.73	3.91	10.47
			C	H	N	
2b	$C_{24}H_{27}O_3N$	Calc :	76.36	7.21	7.71	
		Found	76.23	7.15	3.63	

Martin's spiroannulation[15] using a morpholino enamine was very tempting but unfortunately failed[16] and forced us to go back to the Robinson annulation.

Since the Darzens condensation often used to go from **4** to **13** did not give reproducible yields in our case we better applied the Wittig enol ether sequence[14b,21] for which both steps proved to be very high yielding (Scheme 4). The Robinson annulation then gave the expected spiro enones **2**, albeit in low yields,[17] as a mixture of diastereoisomers.[18] Finally **3a** was obtained by DDQ oxidation of **2a** in 35% yield.

The three compounds **2a**, **2b** and **3a** are devoided of any CNS activity.

EXPERIMENTAL

M.ps were observed on a Reichert apparatus and are uncorrected. Proton NMR spectra were recorded on a Brucker WP 80 spectrometer: Chemical shifts (δ, ppm) quoted in the case of multiplets are measured from the approximate center. Ir spectra were obtained on a Perkin–Elmer 397 spectrophotometer. Microanalytical determinations were made by ATX SA Nanterre (France). Mass spectra were taken on a Varian Mat 311 spectrometer at Rennes University.

6,7-Dimethoxyindan-1-one **5b**

Compound **6**[7] (17.8 g; 0.1 mole) was slowly added, under N_2, to a partially molten mixture of 80.1 g (0.6 mole) $AlCl_3$ and 8 g NaCl at 150°.[8] The temp was raised to 170° for 15 min and then to 200° for an additional 15 min. Crushed ice was poured into the reaction vessel and the soln extracted with EtOAc. After conventional washing and drying of the organic phase a crude product was obtained which was recrystallized in toluene yielding 6.6 g (40%) of **7**, m.p. 135–136° (lit.[9]: 137°).

This dihydroxy-indanone (0.984 g: 6 mmol) was dissolved in THF and stirred for 1 hr at room temp with 0.012 mole of NaH as a 80% dispersion in mineral oil. Iodometane (1.704 g; 12 mmol) in THF was then added dropwise and stirring was maintained for 20 min. Addition of water followed by extraction with ether afforded **5b** in 95% yield, which after distillation melted at 43° (lit.[6]: 40–43°).

6,7-Dimethoxyindenone **11b**

(a) To a soln of 0.96 g (5 mmol) of **5b** in 20 ml CCl_4 was added 1.51 g (5 mmol) of 5, 5-dibromo-2, 2-dimethyl-4, 6-dioxo-1,3 dioxane[19] at room temp. After heating the mixture at 75° for 4 hr, sat $NaHCO_3$aq was added. Usual work-up[11] gave 1.20 g of crude **8b** which was purified by column chromatography on silica gel (Toluene 6: EtOAc 1) giving 0.95 g (70%) of pure **8b**: m.p.: 41°; IR (neat νC=O: 1715 cm^{-1}; 1H NMR ($CDCl_3$) 7.1 (2H, AB quartet, J_{AB} = 8 Hz), 4.6 (1H, dd, J: 3.2 and 7.5 Hz) 4.03 (3H,s) 3.9 (3H,s).

(b) Compound **8b** (1 g: 3.7 mmol) and 0.02 g *p*-toluenesulfonic acid (as its monohydrate) were dissolved in 60 ml toluene containing 3 ml ethylene glycol. The resulting mixture was refluxed for 8 hr with azeotropic removal of the water formed. Usual work-up afforded crude **9b** in quantitative yield. It was used in the next step without any purification.

(c) A mixture of 1 g (3.2 mmol) of the above acetal, 0.56 g (5 mmol) of t-BuOK and 15 ml t-BuOH was heated to 90° under vigorous stirring for 3 hr. The protected **10b** was obtained in 75% yield after the usual work-up, m.p. 56°, ^{1}H NMR ($CDCl_3$) δ 6.7 (2H, s), 6.5 (1H, d, J: 5.7 Hz), 5.9 (1H, d, J: 5.7 Hz), 4.21 (4H, m), 3.90 (3H, s), 3.80 (3H, s).

(d) Silica gel, 6 g (MERCK 230 Mesh for column chromatography) were added to a soln of 4.68 g (20 mmol) of **10b** containing 5 drops N HCl. After 30 min stirring at room temp the reaction was worked up according to Conia's procedure[12] giving 3.8 g (100%) of **11b** as orange crystals, m.p.: 58° IR (neat) νC=O: 1700 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.43 (1H, d, J: 5.9 Hz), 6.67 (2H, s), 5.76 (1H, d, J: 5.9 Hz), 4.11 (3H, s) 3.85 (3H, s). Due to its lack of stability, this compound has not been sent for analysis but an accurate mass has been obtained. Calc *m/e*: 190.069 88 Found: 190.0622.

Indenone **11a**

This has been obtained following the above procedure in 78% overall yield starting from the commercially available **5a**. Indenone **11a**, b.p. 63–65° (1 mm) lit.[13]: 61–63° (0.9 mm)

Spiro[cyclohex - 2 - en - 4 - one - 1, 1' - (3' - methylbenzylamino] indane **2a** *and spiro [cyclohex - 2 - en - 4 - one - 1, 1' - (3'-methylbenzylamino - 6',7' - dimethoxy] indane* **2b**

The two spiroindanes **2a** and **2b** have been obtained according to the same procedure which we describe below for **2b**:

(a) A soln of 3.04 g (16 mmol) of **11b** and 3.87 g (32 mmol) N-methylbenzylamine in CCl_4 was heated with stirring at 60° for 18 hr. After evaporation of the solvent, the residue was taken up in 20 ml N HCl. The aqueous soln was washed with ether, neutralized with $NaHCO_3$ and extracted several times with ether. After washing, drying and concentration of the organic extracts one obtained a residue which was purified by column chromatography on silica gel (hexane 7: acetone 3) yielding 4.48 g (90%) of pure **4b**. Its hydrochloride, m.p. 170° (dec); IR (DBr) νC=O: 1700 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.3 (7H, m), 4.5 (1H, dd, J: 5.5 Hz

and 4.5 Hz), 4.00 (3H, s), 3.89 (3H, s), 3.5 (2H, dd), 2.7 (2H, dd, J: 5.5 Hz and 4.5 Hz); Found: C, 65.23; H, 6.22; N, 4.08. Calc for: ($C_{19}H_{22}ClNO_3$): C, 65.61; H, 6.38; N, 4.03%).

The amino indanone **4a**[20] was obtained in 65% yield; m.p.: 61° IR (KBr) ν C=O: 1700 cm^{-1}; ^1H NMR of its hydrochloride (D_2O): δ 8.0 (4H, m), 7.6 (5H, s), 5.5 (1H, broad t; J: (5.4 Hz) 4.4 (2H, s), 3.3 (2H, broad, d, j: 5.4 Hz), 2.8 (3H, s).

(b) Methoxymethyltriphenylphosphonium chloride (2.055 g, 6 mmol) in soln in anhyd DMSO was slowly added to 6 mmol of NaH (as a 80% dispersion in mineral oil) in 5 ml DMSO under stirring.[21] After 30 min a soln of 0.933 g (3 mmol) of **4b** in DMSO was introduced and stirring maintained for 20 hr at room temp. The mixture was then poured onto crushed ice and extracted with ether. After washing and drying the extracts, the ether was removed *in vacuo* leaving a residue which was purified by column chromatography yielding 1.02 g (75%) of **12b** as an oily mixture of stereoisomers which was used in the next step without separation.

The same kind of oily mixture was obtained in 78% yield when the Wittig reaction was performed on **4a** leading to **12a**.

(c) The mixture of compounds **12b** (20 g; 60 mmol) was heated in 450 ml 3.5% methanesulfonic acid at 90° for 4 hr under vigorous stirring.[14b] After cooling, the mixture was washed with ether and $NaHCO_3$ was cautiously added until a basic pH was obtained. Extraction with ether followed by washing and drying of the extract and evaporation of the solvent gave 14.10 g (85%) of the crude **13b** which proved to be unstable and again was used in the next step without further purification.

Utilizing the above procedure, **13a** was obtained in 90% yield from **12a**.

(d) To a cooled soln (10°) of the above aldehyde (13 g; 40 mmol) in 15 ml t-BuOH was added, under N_2, 11.2 g of a 40% soln of TRITON B in MeOH followed by 8.4 g (120 mmol) methylvinylketone. After 5 hr at room temp 30 ml water was added. The resulting aqueous mixture was extracted with ether, the organic phase washed with water, dried ($MgSO_4$) and concentrated *in vacuo* leaving a residue which was purified by column chromatography on silica gel (hexane 4: acetone 1) and by further recrystallization from isopropyl ether affording 3.75 g (25%) of white cristals; m.p. 126°; IR (KBr) νC=O: 1665 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.34 (7H, m), 6.90 (1H, m, J: 9.5 Hz), 6.0 (1H, m, J: 9.5 Hz) 4.57 (1H, m), 3.83 (3H, s), 3.80 (3H, s), 3.55 (2H, dd), 2.5 (6H, m), 2.33 (3H, s); Found: C, 76.23; H, 7.15; N, 3.63; Calc for ($C_{24}H_{27}O_3N$): C, 76.36, H, 7.21; N, 7.71)

The same procedure yielded **2a** in 25% yield: m.p. (as its hydrochloride): 284° (dec); IR (KBr) ν(C=O): 1660 cm^{-1}; ^1H NMR δ 7.35 (9H, m), 6.7 (1H, m, J: 10 Hz), 6.0 (1H, m, J: 10 Hz), 4.6 (1H, m), 3.6 (2H, dd), 2.2 (6H, m), 2.23 (3H, s); Found: C, 74.24; H, 6.73; N, 3.91; Cl, 10.47. Calc. for $C_{22}H_{24}Cl$ NO for its hydrochloride): C, 74.67; H, 6.83; N, 3.96; Cl, 10.02%).

Spiro[cyclo hex-2, 5-dien-4-one-1, 1'-(3'-methyl benzyl amino)] indane **3a**

Compound **2a** (0.95 g; 3 mmol) was dissolved in a mixture of dimethylacetamide (15 ml) and glacial AcOH (2 ml) and heated at 140°. DDQ (2.7 g; 12 mmol) was then added and heating maintained for 20 min. After removal of the solvents *in vacuo* 10 ml of Et_3N was added. Extraction with ether followed by washing the extracts with water and drying over $MgSO_4$ gave, after concentration of the organic phase, a residue which was purified by column chromatography to afford 330 mg (35%) of **3a** as white crystals, m.p. 98°; IR (KBr) νC=O: 1645 cm^{-1}, ^1H NMR ($CDCl_3$) δ 7.36 (9H, m), 7.0 (2H, m, J: 10 Hz), 6.37 (1H, dd, J: 10 Hz and 1.7 Hz), 6.2 (1H, dd, J: 10 Hz and 1.7 Hz), 4.8 (1H, broad t), 3.63 (2H, dd), 2.38 (2H, dd), 2.26 (3H, s). Due to the relative instability of this compound, no satisfactory analysis could be obtained. An accurate mass was determined ($C_{22}H_{21}NO$) *m/e* Calc. 315, 162305, Found: 315, 1607.

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