A Regiospecific Synthesis of 8-Methoxy-1,2,3,4,5,6-hexahydro-1,6-methano-3-benzazocines

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A regiospecific synthesis of the 6-methoxy-1,2,3,4,5,6-hexahydro-1,6-methano-3-benzazocine system is reported.

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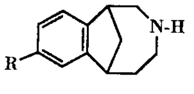
We have previously reported the synthesis (0.12% overall yield) and pharmacological properties of the 1,2,3,4,5,6-hexahydro-1,6-methano-3-benzazocine system **1** [1].



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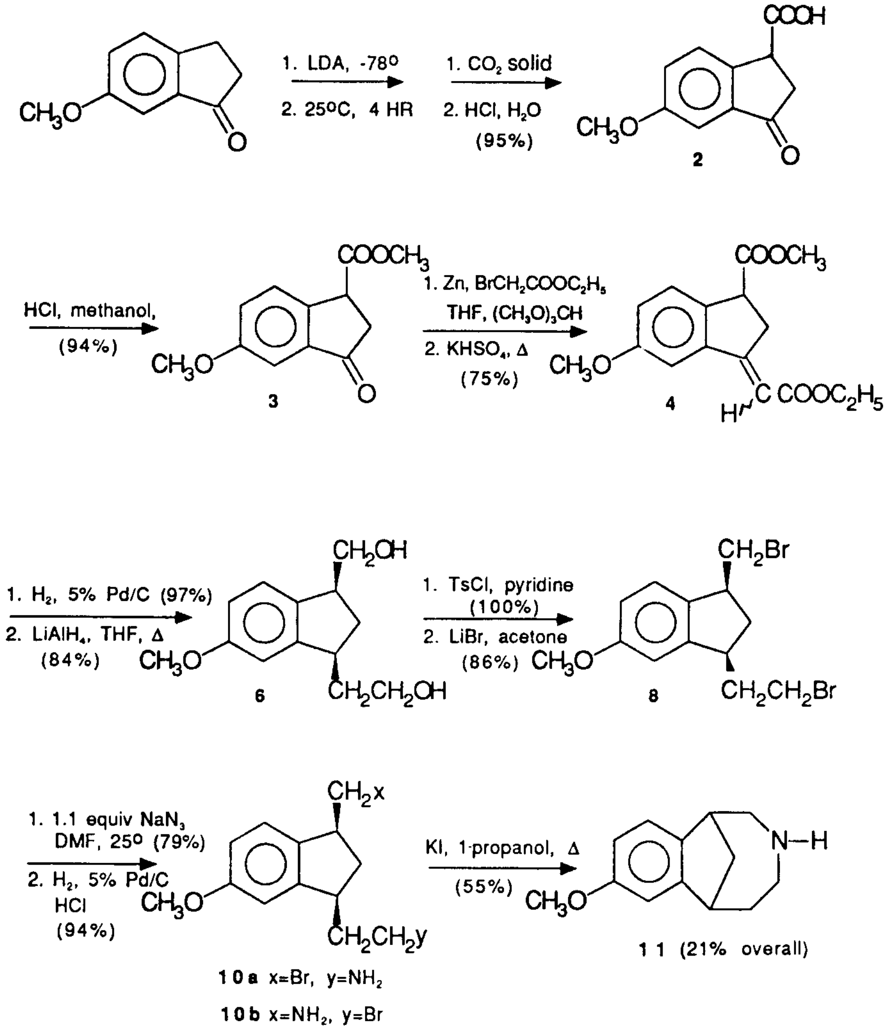
Scheme



An alternative, much improved, synthesis (50% overall yield) which is amenable to scale-up has also been reported [2]. However, both synthetic routes require a difficult and yield-limiting isomer separation when there are substituents on the ring system. Therefore we have developed a completely regiospecific synthesis which is shown in the Sheme. The overall yield of this ten-step synthesis is 21%.

The present route makes use of several published procedures which we have modified to suit our needs. Trost and Latimer [3] generated the lithium stabilized dianion of 6-methoxy-1-indanone using 2.4 equivalents of lithium diisopropylamide in dry tetrahydrofuran to make 3- and 2,3-alkylated 6-methoxy-1-indanones, regiospecifically. We modified this by pouring the dry solution of the dianion over the surface of crushed carbon dioxide solid. The resulting keto carboxylic acid **2** was protected by esterification [4] to **3**. Modification of a Reformatsky reaction using mild conditions [5,6] gave the β-hydroxyester which was dehydrated by distillation from potassium bisulfate to give **4** as a mixture of *syn* and *anti* isomers [7]. Hydrogenation was predicted to occur from the least hindered side of **4** to give the *cis* diester **5**. This prediction was supported by the fact that the ^{1}H nmr of **5** showed only a single ethyl resonance and confirmed by subsequent formation of the target compound **11** (*vide infra*).

To form the ring, diester **5** was reduced [8] to diol **6**, converted to ditosylate **7** and treated with lithium bromide in refluxing acetone [9] to give *cis* dibromide **8**. Treatment of **8** with 1.1 equivalents of sodium azide [10] produced a mixture of isomers **9a** and **9b** which could, without separation, be hydrogenated [11] to isomers **10a** and **10b**, both of which yielded, on closure, the desired product, 8-methoxy-1,2,3,4,5,6-hexahydro-1,6-methano-3-benzazocine (**11**). Ring formation by fewer steps was contemplated by conversion of diester **5** to the corresponding dicarboxylic acid and cyclic imide formation. However, closure to the imide was not successful from the intermediate anhydride [12,13,14], the diacid chloride [15] or directly from **5** [13,16,17,18].

EXPERIMENTAL

6-Methoxy-3-carboxy-1-indanone (**2**).

This compound was prepared by a modification of the procedure of Trost and Latimer [3]. A cold (-78°) solution of 32.45 g (32.1 mmoles, 2.60 equivalents) of diisopropylamine in 250 ml of dry tetrahydrofuran was slowly treated with 18.96 g (29.6 mmoles, 2.40 equivalents), of 1.6 *M n*-butyllithium in hexane. After stirring for 1 hour, 20.00 g (12.3 mmoles) of 6-methoxy-1-indanone in 250 ml of dry tetrahydrofuran was added dropwise over 30 minutes. After stirring an additional hour at -78°, the yellow slurry was allowed to warm to room temperature over 4 hours and siphoned through stainless steel tubing (using positive nitrogen pressure) onto the surface of 300 ml of crushed ice contained in a 2000 ml beaker. Tetrahydrofuran (250 ml) was added, the solution allowed to warm to room temperature overnight and 600 ml of water was added. The aqueous solution was washed with two 150 ml portions of ether, acidified with 20% aqueous hydrochloric acid and extracted with three 250 ml portions of ether. The extracts were combined, washed successively with water, saturated aqueous sodium thiosulfate and brine, dried (magnesium sulfate), filtered and concentrated *in vacuo* to give 24.10 g (95%) of crude **2**. Recrystallization from chloroform-ether gave white material melting at 148.5°-149° whose physical properties and spectral data were identical with those previously reported [4].

6-Methoxy-3-carbomethoxy-1-indanone (**3**).

This compound was prepared using the reported procedure [4] to give 30.12 g (94%) of **3** from 30.01 g of crude **2**.

Ethyl α-(6-Methoxy-3-carbomethoxyindanylidenyl)acetate (**4**).

This compound was prepared using the method of Rathke and Lindert [5]. An 8.92 g (13.65 mmoles) sample of 20 mesh activated zinc [6] was heated under nitrogen and a solution of 30.01 g (13.62 mmoles) of **3** in 45 ml of dry tetrahydrofuran and 45 ml of trimethyl borate added as rapidly as possible. Stirring was initiated and 22.80 g (13.65 mmoles) of freshly distilled ethyl bromoacetate was added. The mixture was heated at 65° with stirring until all the zinc had been consumed (*ca.* 1½ hours). The mixture was cooled, placed in an ice-water bath and hydrolyzed by dropwise addition of a solution of 50 ml of concentrated ammonium hydroxide and 50 ml of glycerol. After separation of the organic phase, the aqueous layer was extracted with three 50 ml portions of ether which were combined, dried (magnesium sulfate), filtered and concentrated *in vacuo* to give 41.70 g (99%) of crude β-hydroxy ester. The crude intermediate was heated over powdered potassium bisulfate at 150° (4.0 mm) for 2 hours and bulb to bulb distilled (bath 205°-230°, 0.70 mm) to give 29.66 g (75%) clear, viscous, red-orange **4** which crystallized on standing. Recrystallization from methylene chloride-hexanes gave pure, tan crystalline **4**, mp 70°-72°; ir (chloroform): 3040, 3020, 3000, 2960, 2840, 1730, 1705, 1640, 1495, 1300, 1185, 1160, 1040 cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 1.1-1.5 (3H, dt), 3.35-4.35 (11H, m), 6.15 (1H, dd), 6.7-7.5 (3H, m).

Anal. Calcd. for $C_{16}H_{18}O_5$: C, 66.20; H, 6.25. Found: C, 66.50; H, 6.50.

Ethyl α-(6-Methoxy-3-carbomethoxy-1-indanyl)acetate (**5**).

A solution of 18.01 g (62.0 mmoles) of **4** in 100 ml of absolute ethanol was hydrogenated for 3 hours over 0.50 g of 5% palladium on carbon in a Parr apparatus at 60 psi. The mixture was filtered through Celite, concentrated *in vacuo* and distilled to give 17.50 g (97%) of colorless **5**, bp 135°-139° (0.20 mm); ir (thin film): 2990, 2960, 2910, 2840, 1735, 1495, 1290-1230, 1210-1140, 1030 cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 1.25 (3H, t), 1.6-3.6 (5H, m), 3.7 (6H, s), 3.8-4.35 (3H, m), 6.4-7.3 (3H, m).

Anal. Calcd. for $C_{16}H_{20}O_5$: C, 65.74; H, 6.90. Found: C, 66.01; H, 7.04.

6-Methoxy-3-hydroxymethyl-1-(2-hydroxyethyl)indan (**6**).

According to the general procedure of Fieser and Fieser [8], a solution of 9.60 g (32.8 mmoles) of **5** in dry tetrahydrofuran was added dropwise with stirring to 1.88 g (49.5 mmoles) of lithium aluminum hydride in 100 ml of dry tetrahydrofuran under nitrogen. The mixture was heated overnight at reflux, cooled and hydrolyzed by successive dropwise addition of 1.9 ml of water, 1.9 ml of 15% sodium hydroxide and 5.7 ml of water. The mixture was stirred an additional 45 minutes, filtered and the solids washed with three 15 ml portions of ether. The combined filtrates were dried (magnesium sulfate), filtered, concentrated *in vacuo* and distilled to give 6.10 g (84%) of yellow, viscous **6**, bath temperature 205°-220° (0.40 mm); ir (thin film): 3600-3100, 2945, 2880, 1500, 1065, 1040 cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 1.2-4.2 (12H, m), 3.75 (3H, s), 6.5-7.3 (3H, m).

Anal. Calcd. for $C_{13}H_{18}O_3$: C, 70.24; H, 8.16. Found: C, 70.24; H, 8.40.

6-Methoxy-3-tosylmethyl-1-(2-tosylethyl)indan (7).

A mixture of 5.70 g (25.6 mmoles) of **6**, 80 ml of dry pyridine and 14.64 g (76.8 mmoles) of dry, recrystallized *p*-toluenesulfonyl chloride was shaken until homogeneous and refrigerated overnight (*ca.* 20 hours at 0°). It was poured into 150 ml of ice-water, acidified with 20% hydrochloric acid and extracted with three 100 ml portions of ether. The combined ether extracts were washed successively with 10% hydrochloric acid, water and saturated sodium bicarbonate, dried (magnesium sulfate), filtered and concentrated *in vacuo* to give 13.0 g (100%) of crude, viscous **7** which was used without further purification; ir (thin film): 3075, 2965, 2845, 1495, 1190, 1175, 1035, 965, 815, 665 cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 0.9-4.5 (19H, m), 6.5-8.0 (11H, m).

6-Methoxy-3-bromomethyl-1-(2-bromoethyl)indan (8).

A solution of 13.40 g (25.3 mmoles) of **7**, (75.0 mmoles) of dry lithium bromide and 80 ml of dry acetone was heated overnight (*ca.* 15 hours) at 80° with stirring [9]. The mixture was cooled to room temperature, poured into 250 ml of water and extracted with three 100 ml portions of ether. The combined ether extracts were dried (magnesium sulfate), filtered and concentrated *in vacuo* to give 8.30 g (95%) of yellow **8**. Recrystallization from hexanes-ether (99:1) gave pure, crystalline **8**, mp 61.5°-63°; ir (chloroform): 3005, 2965, 2845, 1605, 1490, 1290, 1250, 1220, 1150, 1030 cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 1.1-3.95 (10H, m), 3.8 (3H, s), 6.6-7.3 (3H, m).

Anal. Calcd. for $C_{13}H_{16}Br_2O$: C, 44.86; H, 4.63; Br, 45.91. Found: C, 45.15; H, 4.76; Br, 45.50.

6-Methoxy-3-bromomethyl-1-(2-azidoethyl)indan (9a) and 6-Methoxy-3-azidomethyl-1-(2-bromoethyl)indan (9b).

A mixture of 7.52 g (21.6 mmoles) of **8**, 1.41 g (21.6 mmoles) of sodium azide and 40 ml of dry dimethylformamide was stirred at ambient temperature overnight (*ca.* 20 hours). The mixture was poured into 300 ml of water, extracted with three 75 ml portions of hexanes and the combined extracts washed with water, dried (potassium carbonate), filtered and concentrated *in vacuo*. Flash column chromatography [19] of the reaction mixture over Silica Gel 60 gave, on elution with hexanes-ethyl ether (97.5:2.5), 5.31 g (79%) of a mixture of **9a** and **9b**; ir (thin film): 3000, 2960, 2940, 2860, 2025, 1605, 1490, 1300-1200, 1030 cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 1.15-3.95 (10H, m), 3.75 (3H, s), 6.5-7.25 (3H, m).

Anal. Calcd. for $C_{13}H_{16}N_3OBr$: C, 50.34; H, 5.20; N, 13.55; Br, 25.76. Found: C, 50.50; H, 5.39; N, 13.80; Br, 25.97.

6-Methoxy-3-bromomethyl-1-(2-aminoethyl)indan (10a) and 6-Methoxy-3-aminomethyl-1-(2-bromoethyl)indan (10b).

A solution of 1.25 g (40.2 mmoles) of **9a** and **9b** in 50 ml of absolute ethanol and 1 ml of concentrated hydrochloric acid was hydrogenated for two hours at 60 psi over 0.20 g of 5% palladium on carbon in a Parr apparatus. The mixture was filtered through Celite and concentrated *in vacuo*. The residue was dissolved in 50 ml of 5% hydrochloric acid, washed with two 30 ml portions of ether, made basic with 5% sodium hydroxide and extracted with three 50 ml portions of ether. The combined ether extracts were dried (magnesium sulfate), filtered and concentrated to give 1.07 g (94%) of **10a** and **10b**; ir (thin film): 3100-2800, 1605, 1490, 1245, 1025, 780, 755 cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 1.2-4.5 (12H, m), 3.8 (3H, s), 6.6-7.3 (3H, m).

8-Methoxy-1,2,3,4,5,6-hexahydro-1,6-methano-3-benzazocine Oxalate (11).

A solution of 2.98 g (10.5 mmoles) of mixture **10a-10b** in 250 ml of 1-propanol was treated with 1.0 g of finely ground, dry potassium iodide and heated at reflux overnight (*ca.* 20 hours). The mixture was cooled to room temperature, filtered, concentrated *in vacuo* and partitioned between methylene chloride and 5% sodium hydroxide. The aqueous phase was removed and extracted with three 50 ml portions of methylene chloride which were combined with the organic layer, dried (magnesium sulfate), filtered, concentrated *in vacuo* and distilled to give 1.7 g (55%) of **11**. Product **11** was dissolved in ether and ethereal oxalic acid added to give flocculent salt which was recrystallized from methanol-acetone (7:5), mp 208°-210° dec; m/e 203 (M^+-$H_2C_2O_4$); ir (paraffin oil mull): 1720, 1600, 1200 cm^{-1}; ^{1}H nmr (deuterium oxide): δ 1.8-3.7 (10H, m), 3.85 (3H, s), 6.8-7.5 (3H, m).

Anal. Calcd. for $C_{15}H_{19}NO_5$: C, 61.42; H, 6.53; N, 4.78. Found: C, 61.40; H, 6.76; N, 4.49.

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