Synthesis of 1,2,3,4,5,6-Hexahydro-1,6-methano-3-benzazocine

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The synthesis of the title compound was accomplished in 48% yield in five steps from indene.

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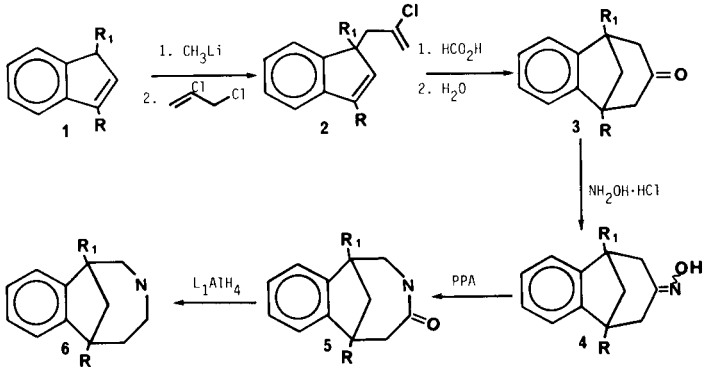
We previously reported the synthesis and pharmacological properties of the 1,2,3,4,5,6-hexahydro-1,6-methano-3-benzazocine system (1). The rather exceptional set of pharmacologic properties that these materials possess led us to investigate an alternative synthetic route which would be amendable to large scale reactions. The previous route involved a photochemical step which, although it took place in moderate yield, was quite difficult to scale up.

The present route involves a simple Beckman rearrangement-reduction sequence on the oxime derived from the tricyclic ketone **3**. Ketone **3** has been previously synthesized by Lansbury, *et al* (2) in 28% yield. Their procedure uses ethyl magnesium bromide as the base in this



a, R = R_1 = H
b, R = CH_3, R_1 = H
c, R = H, R_1 = CH_3

annulation reaction and requires an inverse addition of grignard to the indene. We have found that using methyl lithium as base is more convenient in that inverse addition in not required and the product is formed in improved yield. The simple modification of an already excellent procedure is important in that it also works with 6-methoxyindene where the reaction involving the Grignard as the base completely fails (4). We have also found that careful slow addition of the chloroalkene **2** to the formic acid was beneficial resulting in a 64% overall yield from indene.

Conventional oxime formation using hydroxylamine hydrochloride and sodium acetate afforded the desired oxime in 82% yield. Beckman rearrangement of this material was carried out using polyphosphoric acid in a yield of 94%.

Several reducing agents were tried to carry out the 5 → 6 conversion. We had our greatest success with diborane which accomplished this reaction in 96% yield and the overall yield for this reaction sequence is 48% from indene.

We have also carried out these transformations on methyl indene in the hope that there would be some regio selectivity in the oxime formation, Beckman rearrangement steps affording a preponderance of one of the isomers. Although this sequence is quite efficient (50% overall yield) there is, unfortunately, no convenient separation of the isomers (b,c). We hope to be able to report a complete regio specific synthesis shortly.

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EXPERIMENTAL

3-(2-Chloroallyl)-1-indene (**2**).

This compound was prepared by a modification of the procedure of Lansbury, *et al* (2). A cold (0°) solution of 69.92 g, (0.6019 mole) of indene in 600 ml of anhydrous ether under nitrogen was slowly treated with 13.86 g, (0.6311 mole) of methyl lithium (in ether). The mixture was stirred for 1 hour, cooled to -78° in a dry ice-acetone bath, and treated with 69.83 g, 58 ml, (0.6293 mole) of 2,3-dichloro-1-propene as rapidly as possible. The mixture was warmed to room temperature, stirred for 1 hour, hydrolyzed with saturated ammonium chloride solution, and extracted with three 250 ml portions of ether. The extracts were combined, dried (magnesium sulfate) filtered, concentrated *in vacuo*, and fractionally distilled to give 81.9 g (71%) of **2a**.

3-Oxo-6,7-benzobicyclo[3.2.1]octane (**3a**).

This compound was prepared using the reported procedure (2) to give 26.89 g (91%) of pure **3a** from 32.60 g of **2a**. The use of a syringe pump to introduce **2a** to the reaction mixture resulted in the improved yield.

3-Oximino-6,7-benzobicyclo[3.2.1]octane (**4a**).

A solution of 0.4517 g (6.5 mmoles) of hydroxylamine hydrochloride and 0.8845 g (6.5 mmoles) of sodium acetate trihydrate in 10 ml of water was warmed to 40° and treated with 0.9299 g (5.4 mmoles) of **3a** and 15 ml of methanol. The mixture was heated at reflux for 10 minutes, concetrated *in vacuo* to remove most of the methanol, and extracted with three 10 ml portions of chloroform. The organic layers were combined, dried (magnesium sulfate), filtered, and concentrated *in vacuo*. The resulting residue was recrystallized from hexane-benzene to give 0.80 g (81%) of white, crystalline **4a** (4), mp 161°-162°; ir (potassium bromide): 3460-3020, 2960, 1470, 954, 940, 925, 748 cm^{-1}; ^1H nmr (deuteriochloroform) δ 1.75-3.45 (9H, m), 7.1 (4H, s).

4-Oxo-7,8-benzo-3-azabicyclo[4.2.1]nonane (**5a**).

A mixture of 10.00 g (53.4 mmoles) of oxime **4a** and 100 ml of polyphosphoric acid (Aldrich) in a 1,000 ml beaker equipped with a stirring bar is heated, with stirring to 100°-120°. After stirring at this temperature for 30 minutes the mixture was hydrolyzed by slow, careful addition (exothermic reaction) of ice chips and finally 500 ml of ice water. The aqueous solution was then neutralized with 10% sodium hydroxide solution and extracted with three 250 ml portions of chloroform. The extracts were combined, dried (magnesium sulfate), filtered, and concentrated *in vacuo* to give crude product which was recrystallized from hexanes-benzene to give 9.5 g (95%) of white, crystalline lactam **5a**, mp 183°-184°; ir (potassium bromide): 3285, 3190, 3080-3020, 2925, 1643, 1492, 1470, 762, 750 cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.7-3.8 (9H, m), 7.2 (4H, s).

Anal. Calcd. for $C_{12}H_{13}NO$: C, 76.98; H, 7.00; N, 7.48. Found: C, 76.75; H, 7.00; N, 7.38.

1,2,3,4,5,6-Hexahydro-1,6-methano-3-benzazocine (**6a**).

A 3.20 g (17.1 mmoles) sample of lactam **5a** was dissolved in 125 ml of THF (distilled from calcium hydride) and the solution added at a rapid drop rate with stirring and mild cooling to 80 ml of 1*M* boranetetrahydrofuran complex (Aldrich) under nitrogen. The mixture was refluxed overnight (*ca.* 15 hours), cooled, and hyrolyzed by the dropwise addition of 100 ml of methanol (with stirring and cooling). Dry hydrogen chloride gas was passed through the reaction mixture (**ca.** 5 minutes) until a drop of the reaction mixture turned wet *p*H paper red. The mixture was then refluxed 1 hour, cooled and concentrated *in vacuo*. To the residue was added 20 ml of 20% sodium hydroxide and, after cooling, 70 ml of ether. The layers were separated and the aqueous layer extracted with 50 ml of ether. The combined ether extracts were dried (magnesium sulfate), filtered, and treated with dry hydrogen chloride to give the hydrchloride salt. The hydrchloride salt was recrystallized from methanol-acetone (1:3) to give 3.44 g (96%) of pure **6a** hydrochloride whose physical properties and spectral data were identical with those of an authentic sample (1).

1- and 3-Methyl-3-(2-chloroallyl)-1-indenes (**2b** + **2c**).

The procedure used for the preparation of **2a** was used to afford a 3:1 ratio of **2b**:**2c** in 84% yield, bp 65°-92° (0.20 mm); ir (thin film): 3062, 3040, 3020, 2972, 2938, 2910, 1631, 758, 745, 630 cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.3 (1H, s), 2.1 (3H, s), 2.15-4.0 (3H, m), 4.7-5.6 (2H, dd), 6.0-6.8 (1H, m), 7.2 (4H, s).

Anal. Calcd. for $C_{13}H_{13}Cl$: C, 76.28; H, 6.40; Cl, 17.32. Found: C, 76.53; H, 6.18; Cl, 17.29.

1-Methyl-3-oxo-6,7-benzobicyclo[3.2.1]octane (**3b**).

Reaction of the mixture of **2b** + **2c** with 97% formic acid as previously described for **2a** gave **3b** in 89% yield, bp 80°-86° (0.17 mm) which crystallized on standing. Recrystallization from benzene-hexanes gave pure, white, crystalline **3b**, mp 76°-77°; ir (deuteriochloroform): 3018, 2960, 2875, 1710, 1475, 1460, 1405, 1380, 1330, 1085, 1020 cm^{-1}; ^1H nmr (deuteriochloform): δ 1.38 (3H, s), 1.8-2.8 (6H, m), 3.25-3.65 (1H, m), 7.05 (4H, s).

Anal. Calcd. for $C_{13}H_{14}O$: C, 83.80; H, 7.60. Found: C, 83.98; H, 7.71.

1-Methyl-3-oximino-6,7-benzobicyclo[3.2.1]octane (**4b** + **4c**).

The procedure used for the preparation of **4a** was used for the preparation of **4b** and **4c**. Recrystallization from benzene-hexanes (9:1) gave 4.75 g (88%) of white, crystalline oximes **4b** and **4c** from 5.0 g of **3b**, mp 172.5°-173°; ir (deuteriochloroform): 3500-2700, 1470, 1450, 1020, 940, 915, 750, 725 cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.49 (3H, s), 1.65-3.45 (7H,m), 7.0 (4H, s), 8.62 (1H, s).

Anal. Calcd. for $C_{13}H_{15}NO$: C, 77.58; H, 7.51; N, 6.86. Found: C, 77.88; H, 7.51; N, 6.86.

6- and 1-Methyl-4-oxo-7,8-benzo-3-azabicyclo[4.2.1]nonane (**5b** + **5c**).

The conditions and workup employed for the preparation of **5a** was used. From 1.00 g (5.0 mmoles) of oximes **4b** + **4c** was obtained 0.87 g (86%) of lactams **5b** + **5c** in a 50/50 ratio, after recrystallization from benzene-hexanes (9:1), mp 115°-117°; ir (potassium bromide): 3280, 3190, 3060, 2920, 2875, 1700, 1495, 1480, 755 cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.35 (3H, s), 1.65-3.70 (7H, m), 6.25 (1H, s), 7.1 (4H, s).

Anal. Calcd. for $C_{13}H_{15}NO$: C, 77.58; H, 7.51; N, 6.96. Found: C, 77.49; H, 7.58; N, 6.76.

Attempts to separate the **4b** + **4c** and **5b** + **5c** mixtures by recrystallization and chromatography were fruitless.

REFERENCES AND NOTES

(1) P. H. Mazzocchi and A. M. Harrison, *J. Med. Chem.*, **21**, 238 (1978).

(2) P. T. Lansbury, R. J. Nienhouse, D. J. Scharf and F. R. Hilfiker, *J. Am. Chem. Soc.*, **92**, 5649 (1970).

(3) P. H. Mazzocchi and E. W. Kordoski, unpublished results.

(4) K. Kotera, K. Kitahonoki, Y. Takano and A. Matsuura, *Tetrahedron*, **25**, 335 (1969).