Synthesis of 6-Phenyl-3-azabicyclo[4.2.1]nonane

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The synthesis of the title compound was achieved in five steps in 19% overall yield. The key step was an intramolecular Mannich reaction.

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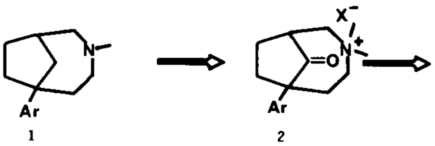
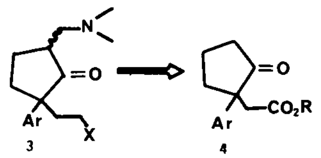
As part of our program investigating the pharmacological properties of a group of compounds we term truncated morphines [1] we required a reasonable synthesis of the 6-aryl-3-azabicyclo[4.2.1]nonane [**1**) ring system. With a route to **1** in hand we would be able to prepare appropriate derivatives for pharmacological testing.

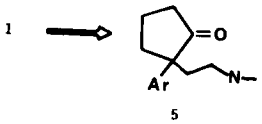
We considered two synthetic approaches to **1**. The first of these involved intramolecular quaternization of the intermediate **3** and subsequent demethylation and reduction of **2**.





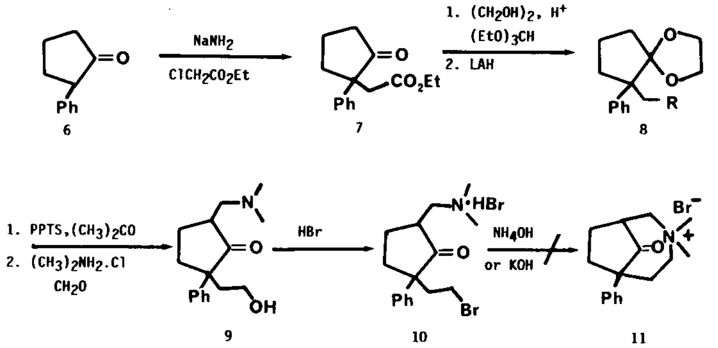
We envisioned that conversion of the ester in **4** to the required carbon containing a leaving group and a Mannich reaction to insert the methylamine substituent should yield the desired **3**. Compound **4** could easily be obtained by alkylation of a 2-arylcyclopentanone [2]. A key point in the synthesis is the stereochemistry of **3** which must obviously have the aryl and aminomethyl substituents *trans* to allow closure. It was our hope that if we ran the ring closure under basic conditions, epimerization of the key center α to the carbonyl would occur giving a sufficient concentration of **3** with the required stereochemistry to effect closure. As we shall see this hope was not realized.

Our second approach, outlined in Scheme 2, involves, an intramolecular Mannich reaction on **5** which may also be obtained, in principle, by alkylation of a 2-arylcyclopentanone [2].



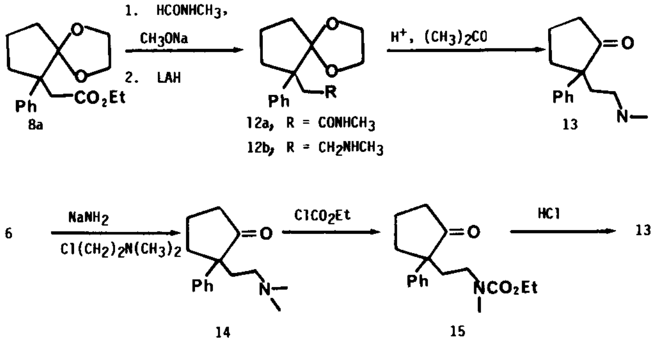
Results.

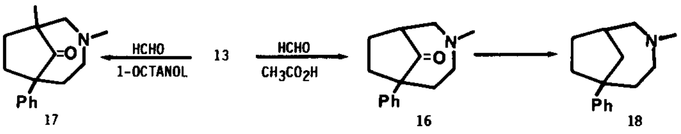
Our initial efforts involved the synthesis outlined in Scheme I. Thus alkylation of the enolate of 2-phenylcyclopentanone [2] using sodamide and ethyl chloroacetate was achieved in 70% yield. The alkylated product **7** was protected as the ethylene ketal **8a** and reduced with lithium aluminum hydride to give the desired alcohol **8b** in an overall yield of 81% from **7**.



Deprotection of **8b** and a Mannich reaction gave **9** in (89% yield from **8**) which was converted to the bromide **10**, using 48% hydrobromic acid [3], in 68% yield. At this point closure of **11** was attempted to no avail using either ammonium hydroxide or 10% potassium hydroxide in a variety of cosolvents. We were unable to detect any of the desired **11** from these reactions. Presumably the bromoethyl and aminomethyl substituents prefer the nonreactive *trans* configuration or the *e,e cis* conformation.

Our second approach started with the now available **8a**. Transamidation using the conditions of Allred and Hurwitz [4] (*N*-methylformamide and sodium methoxide) followed by lithium aluminum hydride reduction and deprotection gave **14** in 57% yield from **15**. A more efficient route to **13** from **6** was developed which involved alkylation of **6** with 2-(*N,N*-dimethylamino)-1-chloroethane and sodamide, conversion of **14** to the carbamate **15** using ethyl chloroformate, and hydrolysis-decarboxylation to **13**. The overall yield from **6** was 73%, considerably better than the 34% overall yield from **6** achieved in the first route. Our first attempt at a Mannich reaction on **3** utilizing the condition of Olson and coworkers [5], which involved heating in 1-octanol to 175°, did not yield the expected product **16**. Instead this reaction produced a single product in 31% yield whose mass spectrum [m/e 243(M+)] and elemental analysis indicated that it was a homolog of the expected **16** containing an additional methylene group. The nmr spectrum showed an unexpected methyl singlet at δ 1.1 which we ascribe to a methyl group on a quaternary carbon whereas the infrared carbonyl absorption at 1740 cm^{-1} indicated that the cyclopentanone ring was intact. We tentatively suggest that this product is **17** on the basis of this evidence although furthe studies are required to definitively establish this structure. We can suggest no reasonable mechanistic route for the formation of the proposed **17**.





Since it is known that Mannich reactions at high temperature often result in significant side reactions [6], we next attempted the Mannich reaction in acetic acid at 100°. This reaction at the lower temperature gave a 33% yield of **13** as a colorless oil which was converted to **18**, the *N*-methyl derivative of **1**, by a Wolf-Kishner reaction in triethylene glycol in 75% yield. The overall yield from **6** in 5 steps was 19%. This synthesis of **18** in good yield allowed us to evaluate derivatives of **18** for pharmacological activity. These results will be published in due course elsewhere.

EXPERIMENTAL

2-Carbethoxymethyl-2-phenylcyclopentanone (7).

To a suspension of 13.4 g (333 mmoles) of sodium amide in 200 ml of dry benzene was added dropwise 51.5 g (322 mmoles) of 2-phenylcyclopentanone in 100 ml of dry benzene under nitrogen. The mixture was refluxed for 5 hours, cooled down with ice-water bath, and 34.5 mℓ (322 mmoles) of ethyl chloroacetate added over 0.5 hours. After stirring at room temperature overnight, the reaction mixture was refluxed for 3 hours, cooled, and treated with 300 ml of cold water. The organic layer was separated, the aqueous layer was extracted with ether, and the combined organic extracts were dried (magnesium sulfate). Solvents were evaporated *in vacuo* and the residue was distilled to give 55.4 g (70%) of compound **7**, gp 136-138° at 1.3 mm Hg; ir (thin film): 3050, 3010, 1730-1740, 1605, 1500, 1450 cm^{-1}; ^{1}H nmr (deuteriochloroform): 1.0-1.2 (t, 3H), 1.3-1.6 (m, 6H), 2.68 (s, 2H), 3.6-4.1 (q, 2H), 7.2 (s, 5H).

Anal. Calcd. for $C_{15}H_{18}O_3$: C, 73.15; H, 7.37. Found: C, 73.40; H, 7.57.

1-Carbethoxymethyl-2-ethylenedioxo-1-phenylcyclopentane (**8a**).

A mixture of 12.6 g (51 mmoles) of compound **7**, 16.7 ml of ethylene glycol, 34 ml of triethylorthoformate, and 0.2 g of *p*-toluenesulfonic acid was heated to 160-165° for 5 hours. The reaction mixture was cooled, 200 ml of petroleum ether (bp 35-60°) was added, and the mixture washed with saturated sodium bicarbonate, brine, and dried (magnesium sulfate). Solvents were evaporated *in vacuo* and the resulting oil distilled to give 12.7 g (86%) of compound **8a**, bp 156-158° at 1.3 mm Hg; ir (thin film) 3060, 3030, 2980, 1750, 1730, 1605, 1505, 1450 cm^{-1}; ^{1}H nmr (deuteriochloroform): 8-1.0 (t, 3H), 1.6-3.0 (m, 8H), 3.1-3.9 (m, 6H), 6.8-7.3 (m, 5H).

Anal. Calcd. for $C_{17}H_{22}O_4$: C, 70.32; H, 7.64. Found: C, 70.04; H, 7.64.

2-Ethylenedioxo-1-(2-hydroxyethyl)-1-phenylcyclopentane (**8b**).

A solution of 32.1 g (110 mmoles) of **8a** in 100 ml of anhydrous ether was added dropwise to 4.35 g (115 mmoles) of LAH in 500 ml of dry THF. The mixture was refluxed for 15 hours, cooled, treated with 9 ml of cold water, 9 ml of 15% potassium hydroxide, 27 mℓ of cold water and stirred overnight. The reaction mixture was filtered, dried (magnesium sulfate), solvent was evaporated *in vacuo* and the residue was distilled to give 26.1 g (95%) of compound **8b** bp 145-146° at 1 mm Hg; ir (thin film): 3400, 3070, 3030, 2950, 2890, 1605, 1500, 1450 cm^{-1}; ^{1}H nmr (deuteriochloroform): 1.4-1.7 (m, 9H), 3.0-4.2 (m, 6H), 7.0 (s, 5H).

Anal. Calcd. for $C_{15}H_{20}O_3$: C, 72.55; H, 8.12. Found: C, 72.67; H, 8.14.

2-(2-Hydroxyethyl)-2-phenylcyclopentanone.

A mixture of 26.1 g (90 mmoles) of **8b**, 10 g (40 mmoles) of pyridinium *p*-toluenesulfonate [7] and 600 ml of wet acetone was stirred at reflux. Solvents were evaporated on a rotary evaporator, dissolved in ether, washed with sodium bicarbonate and brine, and dried (magnesium sulfate). Solvent was evaporated and the resulting oil was bulb to bulb distilled to give 17.4 g (94%) of the unprotected ketone, bp 156-158° at 1 mm Hg; ir (thin film): 3490, 3050, 2950, 2880, 2730, 1605, 1495, 1445 cm^{-1}; ^{1}H nmr (deuteriochloroform): 1.1-2.8 (m, 9H), 3.1-3.5 (t, 2H), 7.2 (s, 5H).

Anal. Calcd. for $C_{13}H_{16}O_2$: C, 72.44; H, 7.89. Found: C, 76.62; H, 8.18.

2-(2-Hydroxyethyl)-5-(*N,N*-dimethylaminomethyl)-2-phenylcyclopentanone (**9**).

In a 250 mℓ round-bottom flask were placed 6.46 g (32 mmoles) of the ketone, 5 g (62 mmoles) of dimethylamine hydrochloride and 2.88 g (32 mmoles) of paraformaldehyde. After addition of 1 mℓ of concentrated hydrochloric acid in 50 ml of 95% ethanol, the mixture was heated at reflux for 4 hours. Solvent was removed *in vacuo*, the residue was treated with 10% sodium hydroxide to *p*H 11, extracted with ether and the ether extracts were washed with water, brine, and dried (magnesium sulfate). Evaporation of solvent gave **9** as an oil (5.67 g, 69%). Attempts at vacuum distillation of **9** resulted in decomposition.

2-(2-Bromoethyl)-5-(*N,N*-dimethylaminomethyl)-2-phenylcyclopentanone Hydrobromide (**10**).

To the crude Mannich base **9** (3.1 g, 12 mmoles) was added 50 mℓ of 48% hydrobromic acid for 1 hour with ice-cooling. The mixture was heated to 100° overnight, solvent reduced to a small volume *in vacuo*, and the dark residue was crystallized from acetone to give 3.27 g (68%) of light gray crystals, mp 157-158°; ir (potassium bromide): 3020, 2960, 2930, 2670, 1730, 1600, 1480 cm^{-1}; ^{1}H nmr (deuteriochloroform): 1.8-3.5 (m, 18H), 7.36 (s, 5H).

Anal. Calcd. for $C_{16}H_{23}NOBr_2$: C, 47.43; H, 5.72; N, 3.46. Found: C, 47.49; H, 5.89; N, 3.48.

1-(*N*-Methylcarbamidomethyl)-2-ethylenedioxo-1-phenylcyclopentane (**12a**).

In a 100 mℓ three-necked, round-bottomed flask a mixture of 12.03 g (41.1 mmoles) of ester **8a**, 2.4 ml (41.4 mmoles) of *N*-methylformamide, and 0.3 g (5.5 mmoles) of sodium methoxide were stirred and heated at 145-150° overnight. The reaction mixture was distilled *in vacuo* to give 9.62 g (84%) of the amide **12a** which solidified at room temperature, bp 152-154° at 0.7 mm Hg; ir (potassium bromide): 3240, 3060, 2960, 2880, 1630, 1460 cm^{-1}; ^{1}H nmr (deuteriochloroform): 1.5-3.0 (m, 11H), 3.2-4.1 (m, 4H), 4.3-4.9 (broad s, 1H), 7.0-7.5 (m, 5H).

Anal. Calcd. for $C_{16}H_{21}NO_3$: C, 69.79; H, 7.69; N, 5.09. Found: C, 69.78; H, 7.80; N, 4.91.

2-(*N*-Methylaminoethyl)-2-ethylenedioxo-1-phenylcyclopentane (**12b**).

A solution of 1.97 g (7.15 mmoles) of **12a** in 50 mℓ of dry THF was added dropwise to 0.42 g (11 mmoles) of LAH in 50 mℓ of dry THF. The mixture was stirred at reflux overnight, cooled, treated with 1 ml of cold water, 1 ml of 15% potassium hydroxide, 3 mℓ of cold water and stirred overnight. The reaction mixture was filtered, dried (potassium carbonate), solvent was evaporated *in vacuo* and the resulting oil was bulb to bulb distilled (bath temp. 195-200° at 0.5 mm Hg) to give 1.34 g (72%) of compound **12b**; ir (thin film): 3100, 3060, 3020, 2960, 2880, 1605, 1500, 1475, 1450 cm^{-1}; ^{1}H nmr (deuteriochloroform): 0.8 (s, 1H), 1.5-2.5 (m, 13H), 3.2-4.0 (m, 4H), 7.0-7.5 (m, 5H).

Anal. Calcd. for $C_{16}H_{23}NO_2$: C, 73.53; H, 8.87; N, 5.36. Found: C, 73.54; H, 9.03; N, 5.56.

2-(2-*N*-Methylaminoethyl)-2-phenylcyclopentanone hydrochloride (**13**). Method (A).

A solution of 12.9 g (43.4 mmoles) of **12b**·HCl, 100 mℓ of wet acetone, and 1 mℓ of 12*N*-hydrochloric acid was refluxed overnight. The reaction mixture was concentrated on a rotary evaporator to give brownish gummy material which was recrystallized from acetone to give **13** as white needles (10.5 g, 95%), mp 126-127°; ir (potassium bromide): 3040, 2960, 2740, 2460, 1740, 1600, 1440 cm^{-1}; ^{1}H nmr (deuteriochloroform): for free amine 1.7-3.7 (m, 10H), 2.65 (s, 3H), 4.1 (br s, 1H), 7.25 (s, 5H).

Anal. Calcd. for $C_{14}H_{20}ClNO$: C, 66.26; H, 7.94; N, 5.52. Found: C, 66.37; H, 8.10; N, 5.30.

Method (B).

A solution of carbamate **15** (30.7 g, 106 mmoles) in 12*N*-hydrochloric acid (250 ml) was heated to 120-130°) for 20 hours, solvent was evaporated *in vacuo* and the residue was recrystallized from acetone to give 26.7 g (100%) of compound **13**.

Attempted Closure to 3-Methyl-9-oxo-6-phenyl-3-azabicyclo[4.2.1]nonane (**16**). Method (A).

In a 500 ml three-necked round-bottomed flask equipped with a stirrer, thermometer, and distillation head were placed 1-octanol (200 ml), compound **13** (3.85 g, 15 mmoles), 0.5 ml of 12*N*-hydrochloric acid and 4.7 g (52.1 mmoles) of paraformaldehyde. The mixture was heated to boiling and the water liberated was removed by distillation until the reaction mixture reached to 175°. After the liberation of water, the mixture was refluxed for another 1 hour, 1.41 g (15.7 mmoles) of paraformaldehyde was added, and the dark reaction mixture was cooled down and poured into water. The aqueous layer was separated, the octanol layer was extracted with 5% hydrochloric acid, the combined aqueous layer was washed with chloroform, made basic to *p*H 11 with ammonium hydroxide, and again extracted with chloroform. The combined extracts were washed twice with brine, dried (magnesium sulfate) and bulb to bulb distilled (bath temperature 210-220° at 0.7 mm Hg) to give 1.13 g of viscous liquid; ms: m/e 243 (M+ -HCl) which indicates $C_{16}H_{21}NO$ is molecular formula of the compound obtained; ir (thin film) 3060, 3020, 2950, 2870, 1740 (cyclopentanone carbonyl group), 1600, 1500, 1460 cm^{-1}; ^{1}H nmr (deuteriochloroform): 1.1 (s, 3H), 1.6-2.9 (m, 10H), 2.4 (S, 3H), 7.2 (s, 5H). The free amine was converted to hydrochloride salt, mp 194-195° dec.

Anal. Calcd. for $C_{16}H_{22}ClNO$: C, 68.68; H, 7.93; N, 5.01. Found: C, 68.27; H, 8.14; N, 4.96.

The spectroscopic data and elemental analysis, suggest that the product has structure **17**.

Method (B).

A mixture of 18.3 g (72 mmoles) of compound **13**, 6 ml of 37% formaldehyde in 300 ml of acetic acid was heated to 100° for 4 hours, 25 ml of 12*N*-hydrochloric acid was added, solvents were evaporated on a rotary evaporator and the resulting oil was extracted with chloroform. The chloroform extracts were dried (magnesium sulfate) and put on a silica gel column (chloroform:methanol = 99:1) to give 4.6 g (33%, based on the starting material consumed) of **16**; ir (thin film): 3050, 3030, 2950, 2800, 1740, 1600, 1500, 1465 cm^{-1}; ^{1}H nmr (deuteriochloroform): 1.4-3.1 (m, 11H), 2.4 (s, 3H), 7.2 (s, 5H). The free amine was converted to hydrochloride salt, mp 191.5-192° dec.

Anal. Calcd. for $C_{15}H_{20}ClNO$: C, 67.79; H, 7.58; N, 5.27. Found: C, 67.69; H, 7.83; N, 5.00.

2-(2-Dimethylaminoethyl)-2-phenylcyclopentanone (**14**).

To a solution of 6.63 g (170 mmoles) of sodium amide in dry benzene (100 ml) was added 24 g (150 mmoles) of **6** in 30 ml of dry benzene and this mixture refluxed for 1 hour under nitrogen. To the mixture 16.2 g (150 mmoles) of 2-dimethylaminoethyl chloride (21.7 g of 2-dimethylaminoethyl chloride hydrochloride was basified with potassium carbonate, extracted with benzene and dried over anhydrous potassium carbonate) and dry benzene was added over 0.5 hours and stirred at reflux overnight. After cooling to room temperature, water was added, the organic layer was separated and the aqueous layer was extracted with ether. The combined organic extracts were washed with 10% hydrochloric acid, made basic to *p*H 11 with ammonium hydroxide and extracted with ether. After drying over magnesium sulfate, solvent was removed on a rotary evaporator, the residue was distilled *in vacuo* to give 20.6 g (80%, based on starting material consumed) of **14**, bp 126-128° at 0.3 mm Hg; ir (thin film): 3060, 3020, 2950, 2820, 2760, 1735, 1600, 1500, 1450 cm^{-1}; ^{1}H nmr (deuteriochloroform): 1.5-2.8 (m, 10H), 2.1 (s, 6H), 7.25 (s, 5H). The free amine was converted to hydrobromide salt, mp 200-201° (acetone).

Anal. Calcd. for $C_{15}H_{22}BrNO$: C, 57.70; H, 7.10; N, 4.49. Found: C, 57.76; H, 7.30; N, 4.48.

2-[(*N*-Carbethoxy-*N*-methyl)aminoethyl]-2-phenylcyclopentanone (**15**).

A solution of 27 g (116 mmoles) of **14** in 150 ml of dry benzene was heated at reflux for 5 minutes, 20.1 g (185 mmoles) of ethyl chloroformate in 50 ml of dry benzene was added over 5.5 hours, and refluxed for 2 hours. The reaction mixture was cooled, washed with 10% hydrochloric acid and brine, and dried (magnesium sulfate). Solvent was evaporated *in vacuo* to give **15** (30.7 g, 91%); ir (thin film): 3030, 2990, 1740, 1700, 1600, 1585, 1500, 1410 cm^{-1}; ^{1}H nmr (deuteriochloroform): 1.2 (t, 3H), 1.6-3.3 (m, 10H), 2.7 (s, 3H), 7.4 (s, 5H).

3-Methyl-6-phenyl-3-azabicyclo[4.2.1]nonane (**18**).

A mixture of compound **16** (3.44 g, 15 mmoles), 95% hydrazine hydrate (3.5 ml) and potassium hydroxide (3.5 g) in 30 ml of triethylene glycol was heated to 165-175° for 4 hours and heated to 185-195° for another 4 hours. After cooling down, the reaction mixture was poured into ice, extracted with ether, washed with water, and dried (magnesium sulfate). Solvent was evaporated on a rotary evaporator and the resulting oil was bulb to bulb distilled to give 2.42 g (75%) of **18**; ir (thin film): 3060, 3020, 2920, 2770, 1600, 1490, 1440 cm^{-1}; ^{1}H nmr (deuteriochloroform): 1.6-3.2 (m, 13H), 2.4 (s, 3H), 7.2 (s, 5H).

The free amine was converted to hydrobromide salt, mp 240-242° dec from ethanol.

Anal. Calcd. for $C_{15}H_{22}BrN$: C, 60.82: H, 7.48; N, 4.73. Found: C, 60.95, H, 7.38; N, 4.54.

Acknowledgement.

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REFERENCES AND NOTES

[1] See for example: P. H. Mazzocchi and B. C. Stahly, *J. Med. Chem.*, **24**, 457 (1981); P. H. Mazzocchi and C. H. Kim, *J. Med. Chem.*, **25**, 1473 (1982).

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