Aza-Ring Expansion of *cis*-Bicyclo[4.2.0]octanones and Related Compounds. A Regiospecific Synthesis of *cis*-Octahydroindolones[1]

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The aza-ring expansion of a series of 1-substituted *cis*-bicyclo[4.2.0]octan-7-ones and related compounds has been examined. Beckmann rearrangement of oximes of the ketones **2**, **6**, and **7** under acid conditions affords as the major products the corresponding octahydroisoindolones **4**, **8**, and **9**, respectively. In contrast to the Beckmann transformations, the *N*-methylnitrones derived from **2**, **6**, and **7** on treatment with *p*-toluenesulfonyl chloride undergo a regio- and stereospecific rearrangement to the respective *cis*-octahydroindolones **13**, **14**, and **20**. The factors responsible for controlling the different regiochemistry exhibited by the Beckmann and nitrone rearrangements in *cis*-bicyclo[4.2.0]octanones and analogous systems are discussed.

In the preceding paper[1] the synthesis of 1-substituted *cis*-bicyclo[4.2.0]octanes has been accomplished in a highly regio- and stereocontrolled manner by a reaction sequence which was initiated through the [2 + 2] cycloaddition of dichloroketene to 1-substituted cyclohexenes.

1-Aryl-*cis*-bicyclo[4.2.0]octan-7-ones derived by this procedure are potentially attractive intermediates for the synthesis of *Sceletium* alkaloids of the mesembrine (**1**)[3] family as well as the more complex *Amarylidaceae* alkaloids of the crinine series.[4]

The elaboration of the 1-aryl-*cis*-octahydroindole (**3**) nucleus of the mesembrine series from the corresponding 1-aryl-*cis*-bicyclo[4.2.0]octan-7-one (**2**) requires an aza-ring expansion (see Scheme I). It is appropriate to note that this transformation requires not only retention of the cis stereochemistry but also that the direction of the ring expansion needs to be controlled in order to avoid the undesired formation of the isoindolin-7-one system **4**.

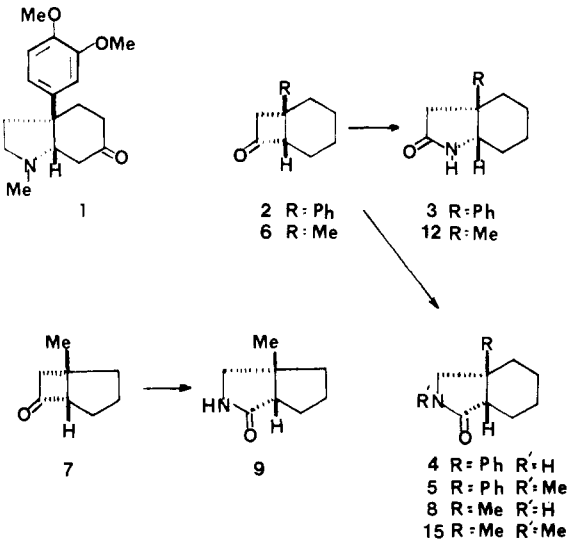
The question of retention vs. inversion of stereochemistry for the ring expansion did not appear to represent a problem since the migration of carbon to electron-deficient nitrogen in derivatives of ketones in the Beckmann and Schmidt reactions normally proceeds with retention of configuration at the migrating carbon center.[5]

With regard to controlling the direction of the ring expansion, the determining factors in the Beckmann rearrangement in most instances is found to depend on the stereochemistry of the oxime whereas in the Schmidt reactions the direction of migration is subject to rather subtle controls which are influenced by both steric effects and migratory apptitudes of the migrating center.[6,7]

Discussion of Results

1-Phenyl-*cis*-bicyclo[4.2.0]octan-7-one[1] gave a single crystalline oxime which on Beckmann rearrangement in polyphosphoric acid, or in P_2O_5–CH_3OSO_3H, afforded a major product which was isolated after chromatography

Scheme I



as a noncrystalline compound and readily identified as a lactam from its IR spectrum (ν_{CO} 1694 cm^{-1}). The ^1H NMR spectral properties of this compound, which showed a 2-proton AB pattern centered at δ 3.32 (J_{AB} = 12 Hz) and a 7-proton multiplet at δ 2.92 was in better agreement with the isoindolone **4** than with the corresponding octahydroindole isomer **3**. Ultimately this structure was firmly supported by its ^{13}C NMR run under the conditions of the INEPT sequence.[8] The sp^3 carbon signal at lowest field occurred at 54.07 ppm in accord with a carbon attached to an amide nitrogen and was shown to originate from a methylene carbon by the INEPT experiment.

Further support for this structural assignment was provided by its conversion to the *N*-methyl lactam **5** and a subsequent comparison of this compound with the isomeric *N*-methyloctahydroindolone **15** obtained by the nitrone-rearrangement pathway (vide infra) which revealed their nonidentity.

An analysis of the Beckmann rearrangement reaction product by GC, and subsequently by GC/MS, indicated that the crude product contained small quantities of the required lactam **3**.

Previous studies[6] have shown that the product distribution of isomeric amides in the acid-catalyzed Beckmann rearrangement is often influenced by reaction temperature. The explanation of this is attributed to the interplay of effects resulting from equilibration of the *E* and *Z* oxime

(1) This paper is part 12 in the series "Sceletium Alkaloids". For part 11 see: Jeffs, P. W.; Molina, G.; Cass, M. W.; Cortese, N. A. *J. Org. Chem.*, previous paper in this issue.
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(6) Tomita, M.; Minami, S.; Uyeo, S. *J. Chem. Soc. C* **1969**, 183. Smith, P. A. S.; Antionides, E. P. *Tetrahedron* **1980**, *9*, 210.
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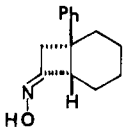
isomers and rates of rearrangement of the latter to isomeric amide products. When the rearrangement of the oxime of **2** was studied as a function of temperature, the ratio of the lactams **3** to **4** was found to increase only marginally from 14:86 to 17:83 over the temperature range 55–190 °C.

These observations indicated that the Beckmann rearrangement of the oxime of the ketone **2** did not appear to offer a practical synthetic route to the octahydroindolone skeleton. However, the rearrangement does provide an excellent synthesis of the isoindolone lactam **4** which was obtained in 94% yield when Eaton's modification[9] using P_2O_5–CH_3OSO_2H was employed.

Similar results were obtained when the oximes of the bicyclic ketones **6** and **7** were subjected to the Beckmann rearrangement in polyphophoric acid. The only products isolated from these reactions proved to be the corresponding isoindolones **8** and **9**.

The formation of the *cis*-octahydroisoindolones in the Beckmann rearrangement of the above-mentioned *cis*-bicyclo[4.2.0]octan-7-ones was most easily rationalized by assuming the stereochemistries of the oximes belong to a single diastereoisomeric series. Although the structure of the rearrangement product suggested that the oxime configuration in these compounds is represented as **10** rather than **11**, this was by no means assured. Not only



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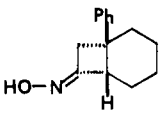

11

was there uncertainty as to whether equilibration of the *E* and *Z* forms occurs prior to rearrangement but also the issue of whether the rearrangement proceeds by an exclusive anti migration process in these cyclobutanone could not be assumed.[10]

In an attempt to clarify this situation, the determination of the stereochemistry of the crystalline oxime obtained from **2** was undertaken by ^1H and ^{13}C NMR studies. Examination of the ^1H spectrum in conjunction with shift differences induced by tris(dipivalomethanato)europium resulted in the H-8α (ΔEu = 2.44 ppm) and H-8β (ΔEu = 2.56 ppm) proton signals being shifted to a greater extent than that of the H-6 proton signal (ΔEu = 2.17 ppm).

From previous studies[11] employing europium shift effects in the ^1H NMR of oximes, complexation on oxygen is preferred to that of nitrogen which led us to conclude that the oxime has the *E* configuration indicated in structure **11**.

Additional evidence for the configuration of the oxime in accord with this view was provided by its ^{13}C spectrum, where a comparison of the ^{13}C shifts[12] of the C-8 methylene and C-6 methine signals in the oxime and the parent ketone **2** indicated a more pronounced upfield shift of the C-8 signal ($\Delta\delta$ = 15.1 ppm) over that of the C-6 carbon ($\Delta\delta$ = 12.9 ppm).

The *E* configuration of the oxime was unexpected since if it rearranges directly by an anti migration process, it should have afforded the octahydroindolone **3**. The fact that the polyphosphoric acid induced rearrangement affords instead the isoindolone **4** is open to several possible explanations which in the absence of definitive information will not be discussed in detail at this time.[13]

In a cursory attempt to seek further informatioin on the Beckmann rearrangement of the oxime **11** under conditioins which would avoid elevated temperatures and acidic conditions, two modifications of the rearrangement were examined. Conversion of the oxime to its tosylate and rearrangement of the latter by passing it over alumina in CH_2Cl_2[15] afforded a 60:40 mixture of the lactams **3** and **4** as determined by GC/MS. A similar result was obtained when the *O*-mesitylsulfonyl oxime, obtained from the ketone **2** and *O*-(mesitylsulfonyl)hydroxylamine,[16] was rearranged in CH_2Cl_2 on an alumina column in that a 65:35 mixture of **3** and **4** was obtained. This latter approach when applied to the bicyclic ketone **6** gave an 85% yield of a mixture of the octahydroindolone/octahydroisoindolone lactams from which the lactam **12** crystallized directly Baeyer–Villiger the mixture in 65% yield. The latter was readily identified from its mass spectral fragmentation pattern (see the Experimental Section) and by the presence of a 1-proton triplet (J = 3 Hz) at δ 3.40 in the ^1H spectrum of **12**. The latter signal is characteristic of the H-7a angular hydrogen in 1-substituted octahydroindolones and related compounds of the mesembrine alkaloid series.[3]

Unless the preparation of the tosylate from the oxime involves an unlikely configurational change around the C=N bond, the previously observed anti specificity of rearrangement of oxime tosylates under these mild conditions[14] must be questioned. Attempts to establish the *E*/*Z* composition of both the oxime tosylate from **2** and its corresponding *O*-mesitylsulfonyl derivative by NMR studies were precluded by the instability of these compounds.

In the single example studied, the Schmidt reaction of **2** afforded in 68% yield a 1:1 mixture of the lactams **3** and **4**.

In work that was being carried out concurrently with our studies, Barton and co-workers[17] showed that *N*-methylnitrones obtained from steroidal ketones undergo ring expansion to the corresponding amides on sequential treatment with tosyl chloride in pyridine and then water.

The significance of this reaction in relation to our needs[18] was their observation that the product obtained from the nitrone rearrangement, in each case, *was the result of migration in the opposite direction from that observed by the Beckmann rearrangement.* A further point of interest regarding the nitrone rearrangement was that diastereoisomeric nitrones derived from a single ketone were shown to rearrange to the same amide.

The reaction of the phenyl-substituted cyclobutanone **2** with *N*-methylhydroxylamine was carried out, and the nitrone was treated in situ with *p*-toluenesulfonyl chloride in pyridine directly without isolation, and after 8 h, water was added to the reaction mixture. The reaction mixture, which showed only starting material and a second component on GC analysis, afforded a lactam (ν_{CO} 1682 cm^{-1}) after column chromatography. The structure of the lactam

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(11) Wolkowki, Z. W. *Tetrahedron Lett.* **1972**, 825.
(12) Levy, G. C.; Nelson, G. L. *J. Am. Chem. Soc.* **1972**, *94*, 4897.
(13) The probability that the *E* oxime is first rearranged to the *Z* isomer is one of several possibilities which can be advanced to explain this result. Other mechanisms which include the possibility of a tetrahedral intermediate[14] or a nitrenium ion[10] cannot be excluded by the information available.
(14) Krow, G. R.; Szezepanski, S. *J. Org. Chem.* **1982**, *47*, 1153.
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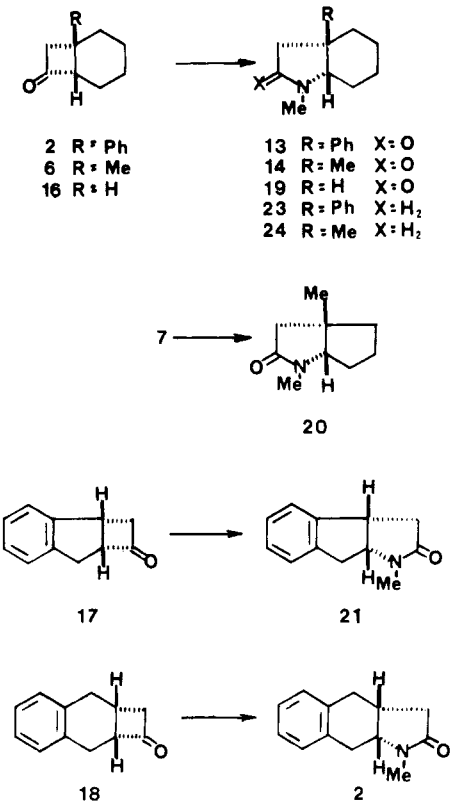
(18) Jeffs, P. W.; Molina, G. *J. Chem. Soc., Chem. Commun.* **1973**, 3.

Scheme II



as the required octahydroindolone **13** (Scheme II) was supported by its ^{1}H NMR spectrum which exhibited a characteristic narrow triplet (J = 3.5 Hz) at δ 3.95 attributable to the H-7a signal.

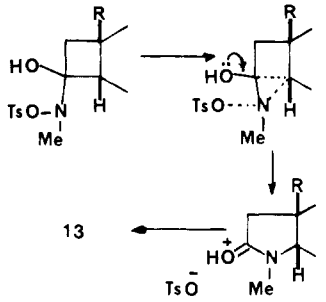
The nitrone from 1-methyl-*cis*-bicyclo[4.2.0]octan-7-one (**6**) when subjected to the same rearrangement conditions similarly afforded the corresponding octahydroindolone **14** as the sole reaction product. Its structure was supported by its ^{1}H NMR which was comparable to that observed for the spectrum of **13** (vide infra).

The specificity in terms of the direction of the nitrone ring-expansion process was confirmed by the rearrangement of the *N*-methylnitrones derived from the bicyclic ketones **16** and **7** and the tricyclic ketones **17** and **18**. From each reaction the only product isolated was the corresponding lactam represented by the structures **19–22**, respectively. The synthesis of the lactam **21** compares to a previously reported unsucessful attempt to effect its synthesis by a Schmidt reaction on the ketone **17**.[19]

A minor limitation to the method as a general procedure for the conversion of cyclobutanones to γ-lactams is that although the percentage conversion is high (>90%), the yield is quite variable, ranging from a low of 40% (**13**) up to 83% (**21**). The variability is most likely dependent upon the extent to which nitrone formation has taken place prior to addition of tosyl chloride. Attempts to drive the reaction to completion by various methods were not entirely successful although addition of 3A molecular series did effect considerable improvement over the original procedure. Fortunately, the balance of material in all these reactions is accounted for by the easy recovery of the starting cyclobutanone which may be recycled if so desired.

The rearrangement of the nitrone also proceeded when acetyl chloride was substituted for *p*-toluenesulfonyl chloride. In these reactions, the yield for the conversion of **2** to **13** was essentially independent of the method used.

Scheme III



A general description of the mechanism of the nitrone rearrangement which accounts for the lack of influence of the nitrone stereochemistry on the direction of the rearrangement has been presented by Barton et al.[17] Further consideration of the examples in the original paper and the additional reactions presented here support the thesis that the regiospecificity observed is exclusively determined by the migratory aptitude of the migrating group. This suggests that the transition state for the ring expansion must occur with the N–O bond having undergone significant separation. The situation may be readily appreciated by comparing the representation of the transition state depicted in Scheme I with the transition state of the well-studied oxygen analogue, the Baeyer–Villiger reaction.[20]

The two lactams **13** and **14** were reduced with $LiAlH_4$ to the corresponding pyrrolidines **23** and **24**, respectively. This not only served as a further characterization of the structures of these compounds but also completed the synthesis of 3a-substituted *cis*-octahydroindoles and provided the basis for attempting the synthesis of alkaloids of the *Sceletium* and *Amaryllidaceae* families by this approach.

Previous mention has been made of the appearance of the H-7a signal in the ^{1}H NMR spectra of *N*-methyl-3a-phenyl-*cis*-octahydroindolone (**4**) and the related lactam **13**. The occurrence of this signal as a narrow triplet (J = 3.5 Hz) is indicative that these compounds exist predominantly, if not exclusively, in a conformation which places the 3a-substituent in an axial position. The similar appearance of the H-7a signal in the two octahydroindoles **23** and **24** indicates that these structures also exist in conformations which place the 3a-substituent in an axial position. The conformational situation for these 3a-substituted octahydroindoles is in full accord with the ground-state conformations found for the closely related compounds represented by *Sceletium* alkaloids of the mesembrine subgroup and the lactone analogues of the *cis*-octahydrobenzo[*b*]furanone series.[1]

Experimental Section

The general procedures and instruments used in this research are the same as reported previously.[1]

1-Phenyl-*cis*-bicyclo[4.2.0]octan-7-one Oxime (11). To a solution of 1 g (14.5 mmol) of hydroxylamine hydrochloride in 6 mL of water were added 163 mg (0.82 mmol) of 1-phenyl-*cis*-bicyclo[4.2.0]octan-7-one (**2**),[1] 4 mL of 10% NaOH, and sufficient alcohol to effect solution, and the solution was heated on a steam bath for 2 h. Extraction with chloroform, drying (Na_2SO_4), and evaporation of the solvent afforded an oil. Crystallization from ether–petroleum ether afforded 95 mg (52%) of **11** as white crystals: mp 115–117 °C; IR 3496 (OH) 1706 cm^{-1} (w, C=N); NMR (80 MHz) δ 7.27 (br s, 5 H, aromatic), 3.54 (br m, 1 H, H-6)

(19) Doyle, P.; Galt, R. H. B.; Pearce, P. J. *Tetrahedron Lett.* **1973**, 2903.

(20) House, H. O. In "Modern Synthetic Reactions", 2nd ed.; W. A. Benjamin: Menlo Park, CA, 1972.

Table I

temp, °C	time	ratio of 3/4	% reaction
55	10 min	10:90	~10
55	72 h	14:86	~50
78	2 h	18:82	~70
145	4 min	22:78	>90
190	1.5 min	26:74	>90

3.15 (dd, 1 H, J = 2.0, 15.1 Hz, H-8β), 2.89 (d, 1 H, J = 15.1 Hz, H-8α) 2.44–1.06 (br m, 8 H, cyclohexyl); ΔEu 2.17 (H-6), 2.56 (H-8β), 2.44 ppm (H-8α); ^{13}C NMR ($CDCl_3$) 158.5 (C-7), 169 (C-1'), 128.2 (C-2', C-6'), 126.1 (C-4'), 125.8 (C-3', C-5'), 47.9 (C-6), 44.6 (C-8), 40.2 (C-1), 38.7 (C-2), 23.8 (C-5), 21.2 (C-3 or C-4), 20.2 ppm (C-4 or C-3); GC/MS (6-ft, OV-17 column, 220 °C) t_R = 3.4 min; mass spectrum, m/e 215 (M^+, 28), 170 (34), 158 (35), 265 (67), 129 (63), 128 (50), 115 (92), 91 (100), 77 (64). Anal. Calcd for $C_{14}H_{17}NO$: C, 78.10; H, 7.96; N, 6.50. Found: C, 77.94; H, 8.07; N, 6.39.

3a-Phenyl-*cis*-octahydroisoindol-1-one (4). (a) The oxime (424 mg, 1.94 mmol) of **2** was mixed well with 10 g of polyphosphoric acid and heated at 53 °C for 21 h. After the reaction was quenched in ice and the mixture extracted with $CHCl_3$ and dried (Na_2O_4), evaporation afforded 364 mg (85%) of an oil. Chromatography in benzene (10 g of grade III alumina) afforded unreacted oxime (211 mg), and then 114 mg of amide **4** (27%), followed by 22 mg of a mixture containing the isomeric amide **3**. Compound **4** was distilled in vacuo at 150 °C (2 mmHg): IR 3184 (NH, w), 1694 cm^{-1} (CO); NMR (60 MHz) δ 7.23 (m, 5 H, aromatic), 6.76 (br, 1 H, NH), 3.27 (s, 2 H, N CH_2), 2.77 (br d, H, H-7a), 2.70–0.77 (complex m, 10 H, cyclohexyl); mass spectrum, m/e (mass spectrum) 215 (91), 158 (100); calcd for $C_{14}H_{17}NO$ m/e 215.1310 (M^+), found m/e 215.1309.

(b) The oxime **11** (25 mg) was immersed in polyphosphoric acid (2 g) in separate experiments at the following temperatures: 190, 145, 78, and 55 °C. Samples (25 μL) were removed periodically, quenched in water, and extracted into $CHCl_3$. Analysis of the concentrates from the $CHCl_3$ extracts were carried out by GC/MS on a 6-ft SE-30 column at 200–250 °C at 10 °C/min. The ratio of the octahydroindolone (**3**; retention time 5.6 min) and the octahydroisoindolone (**4**; retentioin time 6.4 min) was determined from the areas of the peaks as a function of time for each experiment. A summary of the results is shown in Table I.

(c) The oxime **11** (0.108 g, 0.05 mmol) in ether (10 mL) was added to an ice-cold suspension of NaH (0.013 g, 0.052 mmol) in ether (10 mL) under an N_2 atmosphere. After the mixture was stirred for 1 h at 25 °C, *p*-toluenesulfonyl chloride (0.396 g, 0.052 mmol) in ether (15 mL) was added dropwise. The reaction mixture was stirred for 17 h and worked up by pouring it over saturated $NaHCO_3$ solution. The crude tosylate showed complex ^{1}H and ^{13}C NMR patterns. Part of the sample (25 mg) was dissolved in CH_2Cl_2 and passed down an alumina column (5 g, activity I). Elution with CH_2Cl_2 and CH_2Cl_2/MeOH mixtures afforded an oil (18 mg) which was a 60:40 mixture of **3** and **4** by GC/MS (see the *O*-mesitylsulfonyl oxime rearrangement for GC/MS details). The remainder of the crude tosylate decomposed when purification by preparative TLC on silica gel was attempted.

(d) The reagent P_2O_5–CH_3OSO_2H, prepared from CH_3SO_3H (11.84 g) and P_2O_5 (1.3 g) according to Eaton,[9] was placed in a round-bottomed flask and stirred rapidly. The oxime (500 mg) was added in small batches, successive batches not being added until the previous one had dissolved. The total time of addition was on the order of 3 min. The solution was then heated to 100 °C by using an oil bath and maintained at this temperature for 1 h. The reaction was then quenched by adding 50 mL of saturated aqueous $NaHCO_3$, and then the aqueous layer was extracted with CH_2Cl_2. The organic layer was then dried over $MgSO_4$, filtered, and flash evaporated, leaving 486.4 mg (93.2%) of a light brown foam. Purification on a grade III alumina column using 9:1 $CHCl_3$/toluene yielded the pure lactam **4** (392 mg, 79%) which was identical by GC and TLC with the product obtained from the reaction of the oxime with polyphosphoric acid.

3a-Methyl-*cis*-octahydroisoindol-1-one (12). The ketone **6** (500 mg, 3.27 mmol) was converted to the oxime (462 mg, 92%) by the general procedure described for **11**: IR 3610 (OH), 1700 cm^{-1} (w, C=N); NMR (60 MHz) δ 3.0–2.7 (br m, 1 H, angular H), 2.70–2.37 (m, 2 H, cyclobutyl CH_2), 2.37–1.30 (m, 8 H, cyclohexyl), 1.20 (s, 3 H, angular CH_3). The oxime (450 mg, 3.0 mmol) was mixed well with 6.8 g of polyphosphoric acid and heated (in a preheated bath) at 180–185 °C for 2 min. The workup (see above) afforded 253 mg (59%) of the lactam **12** as light yellow crystals. Sublimation [115 °C (7 mmHg) followed by recrystallization from petroleum ether (bp 30–60 °C) gave the pure lactam: mp 123.5–124 °C; IR 3355 (NH), 1686 cm^{-1} (CO); NMR (60 MHz) δ 7.45–6.75 (br, 1 H, NH) 3.01 (s, 2 H, CH_2N), 2.34–2.01 (br m, 2 H, H-7a), 1.81–1.33 (br s, 8 H, cyclohexyl), 1.18 (s, 3 H, CH_3); calcd for M^+ m/e 153.1153, found m/e 153.1144. Anal. Calcd for $C_9H_{15}NO$: C, 70.54; H, 9.87; n, 9.14. Found: C, 70.68; H, 10.08; N, 8.97.

3a-Methyl-*cis*-cyclopenta[*c*]pyrrol-1-one (9). The ketone **7** (84 mg, 0.68 mol) afforded 73 mg (78%) of the corresponding oxime: IR (neat) 3236 (OH), 1698 cm^{-1} (C=N, w).

Ths oxime (73 mg, 0.52 mmol) with 5 g of polyphosphoric at 47 °C overnight on workup gave 37 mg (50%) of the lactam **9**. Bulb to bulb distillation [120 °C (5 mmHg)] afforded an analytically pure sample as a clear liquid: IR 1672 cm^{-1} (CO); NMR (CCl_4, 60 MHz) δ 8.05 (br s, 1 H, NH), 3.18 (s, 2 H, CH_2N), 2.51–1.45 (complex m, 6 H, cyclopentyl), 1.25 (s, 3 H, CH_3); mass spectrum, m/e (relative intensity) 139 (77), 111 (40), 110 (46), 95 (32), 82 (65), 81 (46), 77 (100); calcd for $C_8H_{13}NO$ m/e 139.0997 (M^+), found m/e 139.0990.

2-Methyl-3a-phenyl-*cis*-octahydroisoindol-1-one (5). To a stirred solution of 10 mL of liquid NH_3 were added 450 mg of sodium and one crystal of ferric nitrate. After the blue color disappeared, a solution of 114 mg (0.53 mmol) of lactam **4** in 2 mL of dry ether was added dropwise. After 0.5 h at room temperature, 1.5 mL (24 mmol) of methyl iodide was added and the ammonia allowed the evaporate slowly. Extraction with benzene, drying (Na_2SO_4), and evaporation afforded 67 mg (55%) of an oil. Chromatography in ligroin on alumina (2 g, activity 1) afforded **5** as an oil, which showed a single peak by GC on OV-17 at 250 °C. The NMR spectrum of **5** had no signal at δ 3.9 (unlike the isomeric lactam **16**): IR 1683 cm^{-1}; ^{1}H NMR (60 MHz) δ 7.21 (m, phenyl), 3.20 (s), 2.83 (s, NCH_3), 2.50–0.57 (complex m, cyclohexyl); mass spectrum, m/e (relative intensity 229 (100), 158 (85); calcd for $C_{15}H_{19}NO$ m/e 229.1466 (M^+), found m/e 229.1472.

2,3a-Dimethyl-*cis*-octahydroisoindol-1-one (18). The lactam **10** (104 mg, 0.68 mmol) was methylated with methyl iodide in liquid ammonia as described above to afford 104 mg (92%) of **18**. Chromatography in benzene on alumina (4 g, grade III) provided 42 mg of the pure *N*-methyl amide **18** as an oil which exhibited a single peak by GC on SE-30 at 200 °C: IR (CCl_4) 1696 cm^{-1}; NMR (CCl_4, 60 MHz) δ 2.90 (AB, q, Δ = 11.1 Hz, J = −9 Hz, H-3), 2.77 (s, 3 H, NMe), 2.27–1.23 (complex m, 8 H, cyclohexyl), 1.13 (s, 3 H, CH_3); mass spectrum, m/e (relative intensity) 167 (100), 112 (53), 96 (35), 81 (57), 67 (33), 55 (33); calcd for $C_{10}H_{17}NO$ m/e 167.1310 (M^+), found m/e 167.1313. An analytical sample was obtained by distillation at 100 °C (5 mmHg).

Rearrangement of 1-Phenyl-*cis*-bicyclo[4.2.0]octan-7-one with MSH. A solution of 400 mg (2 mmol) of the cyclobutanone **2** in 5 mL of CH_2Cl_2 was flushed with N_2 and cooled to 0 °C, followed by addition of 450 mg (1.05 equiv) of *O*-(mesitylsulfonyl)hydroxylamine (MSH).[21] Stirring was continued at 0 °C for 1 min, and then the reaction mixture was allowed to warm to room temperature for 1 h. The solvent was removed in vacuo and the residue applied to a column prepared from 12 g of activity I Al_2O_3 (Woelm). The crude mixture of amides was eluted with methanol in nearly quantitative yield and subjected to GC/MS analysis. Separation of the isomeric lactams was achieved on a 2-ft SE-30 column at 220 °C. Identification of the individual components was accomplished by mass spectral comparison with an authentic sample prepared via the Beckmann rearrangement of **2** with methanesulfonic acid and P_2O_5. Thus, the chromatogram obtained from the products of the MSH rearrangement consisted of two peaks identified as 3a-phenyl-*cis*-octahydroisoindol-2-one [retention time 3.6 min; mass spectrum, m/e (relative intensity) 215 (39, M^+) 158 (100), 143 (26), 130 (37), 129 (36), 115 (30), 91 (36)]

(21) Tamura, Y.; Minamikawa, J.; Miki, Y.; Matsugashita, S.; Ikada, M. *Tetrahedron Lett.* **1972**, 4133.

and 3a-phenyl-*cis*-octahydroindol-2-one: retention time 3.9 min; mass spectrum, *m/e* (relative intensity) 215 (52, M^+), 158 (21), 130 (31), 29 (21), 115 (25), 91 (36), 77, (37), 69 (48), 56 (100).

The relative ratio of isooctahydroindolone to octahydroindolone was 43:57, respectively.

Rearrangement of the *O*-Mesitylsulfonyl Oxime of 1-Methyl-*cis*-bicyclo[4.2.0]octan-7-one. A solution of 750 mg (5.4 mmol) of the cyclobutanone **6** was treated with 1.10 g of MSH as described above. Chromatographic workup of the crude oxime mesitylate as previously described gave an 85% yield of a mixture of lactams in an 86:14 ratio by GC/MS. Crystallization of the product from cyclohexane gave a single lactam in 61% recrystallized yield (mp 105–106 °C). NMR analysis showed the product to be 3a-methyl-*cis*-octahydroindol-2-one (**12**): IR 1685 cm^{-1}; ^1H NMR ($CDCl_3$, 100 MHz) δ 6.75 (br s, 1 H br NH), 3.40 (t, 1 H, J = 3 Hz), 2.12 (s, 2 H) 2.0–1.3 (m, 8 H, cyclohexyl), 1.2 (s, 3 H); mass spectrum, *m/e* (relative intensity) 153 (48, M^+), 110 (31), 97 (35), 96 (53), 69 (47), 67 (33), 56 (100), 55 (30), 43 (54), 41 (64); calcd for $C_9H_{15}NO$ *m/e* 153.1153 (M^+), found *m/e* 153.1152.

Schmidt Rearrangement of 1-Phenyl-*cis*-bicyclo[4.2.0]-octan-7-one (2). A solution of hydrazoic acid in $CHCl_3$ was prepared[22] and found to be 1.46 mequiv/mL.

A solution of 2.0 g (10 mmol) of the cyclobutanone **2** in 40 mL of $CHCl_3$ was prepared in a 100-mL round-bottomed flask equipped with a N_2 inlet and magnetic stirrer. A solution of HN_3 in chloroform (8.0 mL, 1.3 equiv) was added at room temperature followed by dropwise addition of 4 mL of concentrated H_2SO_4. Rapid evolution of nitrogen was noted. An additional 1-mL portion of HN_3 solution was added, and the mixture was stirred at room temperature for a total of 6 h. The reaction was quenched by pouring it into cold water, and the aqueous phase was neutralized with saturated $NaHCO_3$. Evaporatioin of the solvent gave 1.46 g (68% yield) of a brown oil. Purification by chromatography on silica gel with chloroform as the eluant gave a mixture of γ-lactams eluting as a single band. ^1H NMR showed an approximately 50:50 mixture of 3a-phenyl-*cis*-octahydroindol-2-one. This conclusion was supported by analysis by GC/MS on a 6-ft SE-30 column and by comparison with authentic samples by GC.

1-Methyl-3a-phenyl-*cis*-octahydroindol-2-one (13). (a) The ketone **2** (500 mg, 25 mmol) and MeNHOH·HCl (1 g) was stirred in 10 mL of pyridine containing 20 pellets of 3A molecular sieves under a N_2 atmosphere for 24 h. *p*-Toluenesulfonyl chloride (1.5 g) was added and stirring continued for 4 h, at which time 2 mL of H_2O was added to the reaction mixture. A workup in the usual way afforded 410 mg (64%) of a dark oil. Analysis by GC on a 6-ft OV-17 column at 245 °C indicated the oil contained 35% of the lactam **13** and 30% of the starting ketone **2**. Chromatography of the crude product in benzene in 10 g of grade III alumina gave 363 mg (32%) of **13** as a viscous oil, which was distilled at 115–120 °C (0.1 mmHg) to give the pure lactam **13**: IR 1682, 1674 cm^{-1}; NMR (CCl_4) δ 7.25 (br s, 5 H, phenyl), 3.95 (t, 1 H, J = 3.5 Hz, H-7a), 2.80 (s, 3 H, NMe), 2.38 (s, 2 H, CH_2CO), 2.30–1.11 (complex m, 8 H, cyclohexyl); mass spectrum calcd for $C_{15}H_{19}NO$, *m/e* 229.1466 (M^+), found *m/e* 229.1470.

(b) The reaction was repeated as above with DMF as a solvent to give **13** in 30% yield.

(c) When the conditions in part a were used, except that Ac_2O was substituted for tosyl chloride, the isolated yield of **13** was 20%.

1,3a-Dimethyl-*cis*-octahydroindol-2-one (14). A mixture of 2.03 g (14.7 mmol) of ketone **6** were treated under nitrogen in the same manner as described for **13** with 1.56 g (18.4 mmol) of *N*-methylhydroxylamine hydrochloride, 10 mL of pyridine, 1.9 g (15 mmol) of tosyl chloride, and 1 mL of H_2O. A workup in the usual manner afforded 2.32 g of dark oil, which was chromatographed in benzene–10% HCl_3 on 20 g of grade I alumina to yield 510 mg (20%) of **33** as a brown oil. Bulb to bulb distillation (95 °C, 5 mmHg) afforded the pure amide **14** as a clear liquid: IR (CCl_4) 1695 cm^{-1}; NMR (CCl_4, 60 MHz) δ 3.11 (t, 1 H, J = 4 Hz, H-7a), 2.73 (s, 3 H, NCH_3), 1.92 (s, 2 H, CH_2–CO), 1.58 (m, 8 H, cyclohexyl), 1.11 (s, 3 H, CH_3); mass spectrum, *m/e* (relative intensity) 127 (70), 111 (50), 110 (50), 81 (54), 69 (76), 57 (92), 55 (100); calcd for $C_{10}H_{17}NO$ *m/e* 167.1310 (M^+), found *m/e* 167.1312.

1-Methyl-*cis*-octahydroindol-2-one (19). Conversion of the ketone **16** (1.09 g, 8.65 mmol) to **19** as described previously for **13** gave a crude product (1.04 g, oil). Purification on 10 g of grade I alumina resulted in 280 mg (21%) of **19** [oil, pure by GC (OV-17, 200 °C)]. Bulb to bulb distillation (95 °C, 2 mmHg) afforded the lactam **19** as a clear liquid: IR (neat) 1697 cm^{-1} (CO); NMR ($CDCl_3$) 3.48 (q, 1 H, J_{app} = 5.0, H-7a), 2.78 (s, 3, NCH_3), 2.20 and 2.11, (2 br s, 2H, CH_2–CO), 1.95–1.20 (complex m, 9, cyclohexyl); mass spectrum, *m/e* (relative intensity) 153 (34), 110 (100); calcd for $C_9H_{15}NO^+$ *m/e* 153.1153 (M^+), found *m/e* 153.1147.

1,3a-Dimethyl-*cis*-hexahydrocyclopenta[*b*]pyrrol-2-one (20). Similarly, ketone **7** (195 mg, 1.6 mmol) was converted by the standard conditions to 180 mg of an oil containing the crude amide **20** and starting ketone (50:50 ratio by GC, 37%). Bulb to bulb distillation (40 °C, 2 mmHg) afforded the pure amide **20** as a clear liquid (after collecting a forerun containing mostly starting ketone): IR (neat) 1684 cm^{-1} (CO); NMR (CCl_4) δ 3.37 (t, 1 H, H-6a, $W_{1/2}$ = 7 Hz), 2.71 (s, 3 H, NCH_3), 2.18 (s, 2 H, CH_2CO), 2.07–1.45 (m, 6 H cyclopentyl), 1.23 (s, 3 H, CH_3); mass spectrum, *m/e* (relative intensity) 153 (72), 111 (94), 110 (100); calcd for $C_9H_{15}NO$ *m/e* 153.1153 (M^+), found *m/e* 153.1158.

3a,4,9,9a-Tetrahydro-1-methylbenz[*f*]indolin-2-one (21). To a room-temperature solution of the ketone **17** (473 mg, 2.75 mmol) in 10 mL of pyridine under nitrogen were added 10–20 3A molecular sieves and 920 mg (11 mmol) of *N*-methylhydroxylamine hydrochloride. After all of the hydrochloride had dissolved, the solution was stirred for 24 h. Then, while the mixture was cooled in ice and stirred, tosyl chloride (600 mg) was added. The reaction mixture was then warmed to room temperature while the stirring was continued. After 5 h, 1 mL of water was added, and stirring was continued overnight. The solution was then repeatedly evaporated with $CHCl_3$, treated with concentrated HCl until it was distinctly acidic, and then extracted with water, and finally the $CHCl_3$ was washed with 10% NaOH, dried over Na_2SO_4, filtered, and flash evaporated, leaving a dark oil. Chromatography of the crude product in 1:1 benzene/chloroform on a 15-g Al_2O_3 (grade II) column afforded 300.6 mg (54.4%) of the desired lactam **21**: IR (neat) 1671.4 cm^{-1}; NMR (60 MHz) δ 7.28 (t, 4 H), 2.80 (s, 3 H), 3.16–2.48 (m, 8 H); calcd for $C_{13}H_{15}NO$ *m/e* 201.1154 (M^+), found *m/e* 201.1148.

2,3a,8,8a-Tetrahydro-1-methylindeno[2,1-*b*]pyrrol-2-(1*H*)-one (22). The ketone **18** (917 mg, 5.81 mmol) in 13 mL of dry pyridine was converted to the crude lactam in 83% yield by the same procedure described in the preceding experiment. Column chromatography on grade III Al_2O_3 afforded the pure lactam **22** upon elution with $CHCl_3$: IR (neat) 1675 cm^{-1}; NMR (60 MHz) δ 7.16 (s, 4 H), 2.92 (s, 3 H), 4.0–3.0 (br m, 6 H); calcd for $C_{12}H_{13}NO$ *m/e* 186.0923 (M^+), found *m/e* 186.0919.

1-Methyl-3a-phenyl-*cis*-octahydroindole Hydrochloride (23). To a stirred refluxing suspension of 160 mg (4.2 mmol) of $LiAlH_4$ in 10 mL of tetrahydrofuran was added a solution of 193 mg (0.84 mmol) of amide **13** in 4 mL of THF dropwise over 0.5 h, and the mixture was refluxed overnight. After the mixture cooled, sufficient 10% NH_4Cl solution was added to destroy the excess reagent. The mixture was filtered, the precipitate was washed well with THF, and the solvent was concentrated to a small volume. Extraction with ether afforded, after drying, 112 mg (62%) of the oily amine **23**: NMR (CCl_4, 60 MHz) δ 7.34 (m, 5 H, aromatic), 3.74–3.0 (complex m, 2 H), 2.60 (t, 1 H, H-7a, $W_{1/2}$ = 6 Hz), 2.20 (s, 3 H, NCH_3), 2.2–1.3 (m, 10 H, cyclohexyl). Addition of $Eu(fod)_3$ as a complexing shift reagent resulted only in simplification of the δ 3.74–3.0 signal to a quartet for one H centered at δ 3.38, with couplings of 15 and 7.5 Hz; the couplings were unaltered at 60 or 90 MHz. No coordination of the Eu on the nitrogen occurred.

The hydrochloride was obtained by addition of concentrated HCl to an ether solution of the indole. Repeated crystallizations from ethanol–ether afforded an analytical sample, mp 244–245 °C (lit.[23] mp 246 °C). Anal. Calcd for $C_{15}H_{22}ClN$: C, 71.54; H, 8.81; N, 5.56. Found: C, 71.66; H, 8.93; N, 5.40.

1,3a-Dimethyl-*cis*-octahydroindole Hydrochloride (24). A solution of 680 mg (4.07 mmol) of amide **14** was reduced by $LiAlH_4$ as described above to afford 262 mg (42%) of crude amine

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(23) Popelak, A.; Lettenbauer, G. U.S. Patent 3 028 394; *Chem. Abstr.* **1962**, *57*, 85497.

as a brown oil: NMR (60 MHz) δ 3.63–2.53 (complex m, 3 H, HC–N–CH_2), 2.37 (s, 3 H, NCH_3), 1.97–1.21 (m, 12 H, cyclohexyl), 0.9 (s, 3 H, CH_3). An analytical sample was obtained by the addition of HCl to an ether solution of the amine, followed by repeated crystallizations from ethanol–ether. The hydrochloride was obtained as a white solid, mp 201–203 °C. Anal. Calcd for $C_{10}H_{20}NCl·0.5H_2O$: C, 60.43; H, 10.65; N, 7.05. Found: C, 60.27; H, 10.68; N, 6.98.

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Registry No. **2**, 39778-70-6; **3**, 82732-39-6; **4**, 39778-77-3; **5**, 82732-43-2; **6**, 39778-69-3; **6** oxime, 39778-89-7; **7**, 5212-68-0; **7** oxime, 82732-42-1; **9**, 82732-41-0; **10**, 82769-24-2; **11**, 82769-23-1; **12**, 82732-40-9; **13**, 39778-79-5; **14**, 39778-78-4; **16**, 27655-70-5; **17**, 31996-70-0; **18**, 82732-32-9; **19**, 1196-52-7; **20**, 39778-84-2; **21**, 82732-44-3; **22**, 82732-45-4; **23**, 82732-46-5; **24**, 82732-47-6; *O*-(mesitylsulfonyl)hydroxylamine, 36016-40-7; *N*-methylhydroxylamine hydrochloride, 4229-44-1.

Synthesis of (±)-Mesembranol and (±)-*O*-Methyljoubertiamine. Aza-Ring Expansion of *cis*-Bicyclo[4.2.0]octanones[1]

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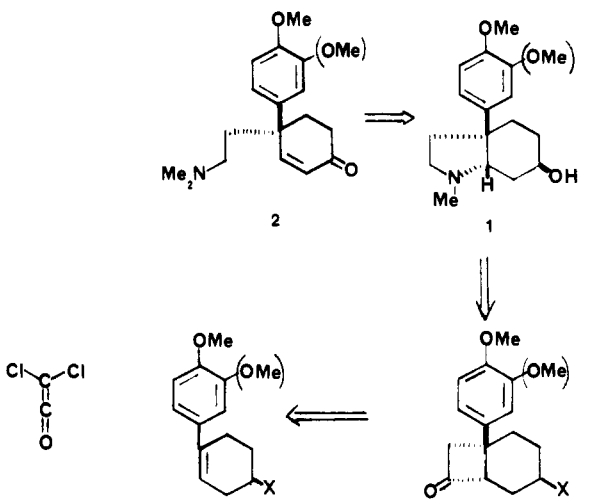
The syntheses of (±)-mesembranol (**1**) and (±)-*O*-methyljoubertiamine (**2**) are described. Each synthesis is developed from a regio- and stereospecific heteroannelation sequence of the respective 1-arylcyclohexenes **4** and **10** to provide the 3a-aryl-*cis*-octahydroindolone skeleton of the mesembrine alkaloid series represented by the intermediates **6** and **14**. The transformation of **6** to (±)-mesembranol is readily accomplished by reduction with diborane and subsequent cleavage of the *O*-benzyl protecting group by hydrogenolysis. Similarly, the octahydroindolone **14** is converted to (±)-*O*-methyljoubertiamine by hydrolysis of the acetate **14** to the alcohol **15**, reduction of **15** with diborane, and oxidation of the resulting 6-hydroxy compound **16** to the ketone **17** which is then converted to (±)-*O*-methyljoubertiamine on reaction with methyl iodide and base.

Isolation and structural studies on alkaloids from *Sceletium* species (family Aizoaceae) carried out in this laboratory during the past 15 years have led to the characterization of some 25 new bases.[2] This family of alkaloids, which belong to four different ring systems, has been the target of considerable effort on the part of several research groups in developing syntheses of representative members. Several of these approaches are elegant both in their concept and generality[3] while, in addition, the recently described synthesis of (±)-mesembrine by Martin provides the alkaloid in good overall yield.[4]

The initial impetus to develop an efficient synthetic procedure was provided by the need for synthetic analogues of mesembrine for conformational studies. In particular, design of the synthetic plan was constructed to permit a rather flexible approach to *cis*-octahydroindoles containing a variety of different substituents at the 3a-position.

The approach which forms the basis of the two syntheses discussed in this report is summarized in retrosynthetic terms in Scheme I. The transformation of this formalism to practice relies on the development of the synthesis of 1-aryl-*cis*-bicyclo[4.2.0]octan-7-ones from 1-arylcyclohexenes and the unidirectional aza-ring expansion of the bicyclooctanones to the 3a-aryl-*cis*-octahydroindoles to

Scheme I



effect what amounts to a regioselective and stereoselective heteroannelation of a carbocycle. The reactions employed which lead to the desired regio- and stereocontrol in the formation of these systems are explicitly defined by previous studies which are reported in the two preceding papers.[1,5] Extension of this particular approach to the synthesis of (±)-mesembranol (**1**)[6] and (±)-*O*-methyljoubertiamine (**2**)[7] constitutes the work described in this paper.

(1) This paper is part 13 in the series "Sceletium Alkaloids". For part 12 see: Jeffs, P. W.; Molina, G.; Cortese, N. A.; Hauck, P. R.; Wolfram, J. *J. Org. Chem.*, previous paper in this issue.

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