Steric Controls in the Preparation of 1-Benzyl-1,4-dihydro-3-(2*H*)isoquinolones and 1-Benzyl-1,2,4,5-tetrahydro(3*H*)-2-benzazepin-3-ones *via* Beckmann Rearrangement

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The effect of substituents in the 1-position of 2-indanones and 2-tetralones on the course of Beckmann rearrangement reactions was studied. Nmr spectral anaylses of the intermediate oximes and final products demonstrated that steric controls were operative both before and during rearrangement. Use of the appropriate substituents and reaction conditions makes this reaction scheme attractive for preparation of the title compounds.

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During the course of studies directed toward the development of a convenient, high-yielding synthetic route for the preparation of 1-benzyl-1,4-dihydro-3-(2*H*)isoquinolones (Va) and the homologous 1-benzyl-1,2,4,5-tetrahydro(3*H*), 2-benzazepin-3-ones (Vc), we examined the potential of incorporating the Beckmann rearrangement into this scheme. The Beckmann rearrangement has long been recognized as an extremely valuable and versatile method for the preparation of lactams (3), however, the literature contains surprisingly few reports dealing with the Beckmann rearrangement of oximes derived from 2-indanones (4,5) or 2-tetralones (6-8) and no investigation of the monosubstituted analogs has ever been made.

One inherent problem frequently encountered in the Beckmann rearrangement of unsymmetrical ketones *via* the intermediacy of an oxime stems from the formation of isomeric lactams. The predominant product is often dictated by the initial oxime isomer ratio. In our investigation, it was reasoned that if the benzyl group was sufficiently large steric interactions may force the development of a preferred oxime configuration, oxime III, which would lead to the desired lactam V as a major component upon rearrangement. If amounts of the minor oxime, oxime IV, could be minimized the potential for a viable synthetic scheme existed (Scheme I).

In order to test this hypothesis, both 1-benzyl-2-indanone (IIa) and 1-benzyl-2-tetralone (IIc) were prepared by an improved enamine alkylation procedure developed in this laboratory (9) and the corresponding oximes subjected to phosphorus pentachloride in chloroform at -50° (10). Encouragingly, the oxime derived from IIa gave lactam Va in 37% yield and the oxime from IIc afforded Vc in a yield of 84%. Most importantly, the nmr of the isolated products established conclusively that only one isomer was formed in each reaction. By observing the multiplicity of the C-1 proton, before and after deuterium exchange, the proper isomer could be identified. For example, the spectrum of Vc showed a five-line pattern at 4.86 ppm which integrated for one proton. The N-H absorption appeared at 6.1 ppm. Upon deuterium exchange the pattern at 4.86 ppm was reduced to a four-line pattern and the absorption at 6.1 ppm disappeared. Calculation of the coupling constants allowed for full interpretation of the pattern. Conformation of all structural assignments was obtained by mass spectral analyses (see discussion which follows).

Examination of nmr spectra of starting materials revealed, however, that while Va was obtained from a single oxime, oxime IIIa, the analogous 3*H*-2-benzazepin-3-one Vc was derived from a 70:30 mixture of IIIc and IVc, respectively. Since no evidence for the formation of VIc could be obtained, it seems likely that isomerization of IVc to IIIc propably took place under the conditions for reaction prior to Beckmann rearrangement (3).

An investigation of derivatives of these compounds sup-

Scheme I

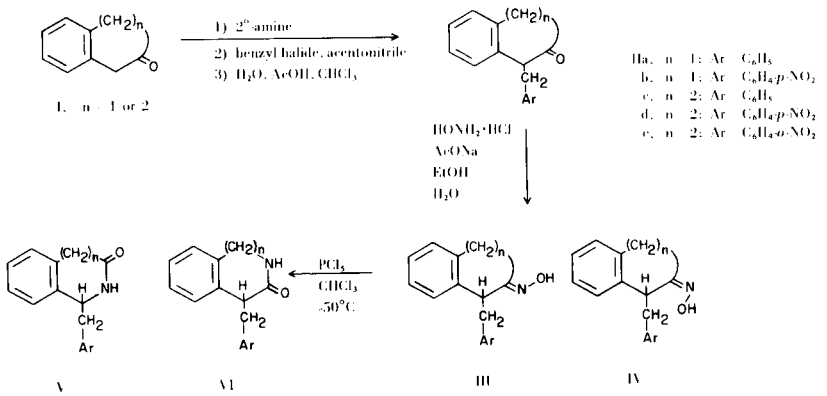


Table 1

Compound	Oxime Isomer Ratio, % (a)	Compound	Lactam Yield, % (b)
IIIa	100	Va	37
IVa	-	VIa	-
IIIb	100	Vb	- (c)
IVb	-	VIb	-
IIIc	70	Vc	84
IVc	30	VIc	-
IIId	50	Vd	64 (a)
IVd	50	VId	36 (a) 58 (b,d)
IIIe	100	Ve	93
IVe	-	VIe	-

(a) Ratios determined by nmr spectroscopy. (b) Isolated yield after purification by recrystallization. (c) Reaction of IIIb with phosphorus pentachloride-chloroform in the usual manner afforded no detectable amounts of Vb or VIb. (d) Mixture of inseparable isomers.

ported the results obtained in our initial experiments. Reaction of IIb with hydroxylamine resulted in the formation of only one isomer, oxime IIIb. In contrast, a 50:50 mixture of IIId and IVd was obtained from IId. Again, proton nmr clearly differentiated IIId and IVd. A double doublet centered at 3.81 ppm was assigned to the C-1 proton of the *anti* oxime IIId and accounted for half of the total oxime while the C-1 proton of the *syn* oxime IVd absorbed as a four-line pattern at 4.55 ppm. Upon reaction with phosphorus pentachloride-chloroform, the equal molar mixture of isomers afforded Vd in 64% and 36% of VId (58% isolated yield). The C-1 proton of lactam Vd absorbed as a six-line pattern at 4.83 ppm and collapsed to a four-line pattern upon addition of deuterium oxide. The C-1 proton of the isomeric lactam VId absorbed as a four-line pattern even after deuterium oxide was added to the sample. The N-H proton absorptions centered at 5.91 ppm and 6.47 ppm disappeared upon addition of deuterium oxide to the sample.

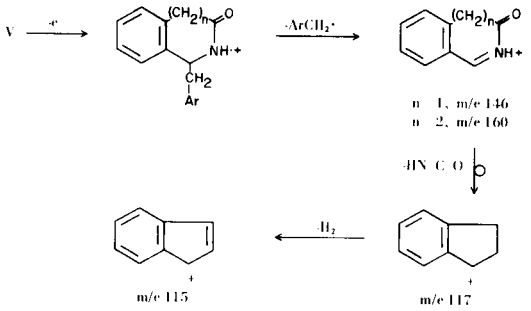
At this point it became apparent that steric controls were operative in our systems, both before and during reaction, with the 2-tetralones less sensitive to steric bulk of 1-substituents than the 2-indanones. Therefore, we next chose to examine the effect on oxime isomer ratios of the small methyl group in 1-methyl-2-idanone oxime (11) and the large *o*-nitrobenzyl substituent in 1-*o*-nitrobenzyl-2-tetralone oxime. Preparation of each compound and subsequent nmr analyses showed that only one *anti* oxime was formed in each case. Furthermore, when IIIe was caused to react with phosphorus pentachloride in chloroform at -50° a 93% isolated yield of Ve was realized. A summary of isomer ratios and isolated yields is presented in Table I.

Based on the considerations mentioned above, the steric effect of 1-substituents in 2-tetralones is clearly evident. As the benzyl group becomes increasingly large a trend toward a preferred configuration is found. Thus an equal molar mixture of isomers is formed from the 1-*p*-nitrobenzyl substituent while only the *anti* oxime IIIe is formed when the bulky 1-*o*-nitrobenzyl substituent is employed. On the other hand, 1-substituted-2-indanones appear to form only one oxime regardless of the size of the substituent; at least, for the substituents which have been studied here. This difference in behavior may be accounted for on the basis of conformational preference about the C-C bond attaching the substituent to the indanone and tetralone ring (12).

As mentioned previously, the mass spectral fragmentation characteristics of the isolated lactams supported the nmr structural assignments. Ionization of the lactams can be visualized as taking place by removal of one of the lone pair electrons, to give upon loss of benzyl radical a resonance stabilized ion in relatively high abundance (*ca.* 60-100%). In the case of 1-benzyl-1,2,4,5-tetrahydro-(3*H*)-2-benzazepin-3-ones, equally important processes which followed involved loss of HN=C=O and H_2 to produce ions with m/e 117 and 115, respectively (relative abundance 30-100%). A plausible reaction path for the genesis of these ions is depicted in Scheme II.

Scheme II

Fragmentation Pathway for 1-benzyl-1,4-dihydro-3-(2H)-isoquinolones and 1-benzyl-1,2,4,5-tetrahydro-(3H)-2-benzazepin-3-ones



EXPERIMENTAL

Melting points were obtained with a Thomas-Hoover melting point apparatus and were uncorrected. Distillations were performed on a Buchi/Brinkman Kugelrohrofen micro-distillation oven and boiling points were uncorrected. Nmr spectra were recorded on a Hitachi Perkin-Elmer R20-B spectrometer equipped with a Nicolet

TT-7 Fourier transform accessory and are reported in parts per million down field from tetramethylsilane as an internal standard. Deuterium exchange experiments were performed using deuterium oxide containing a small amount of dissolved sodium. A Du Pont model 21-491 mass spectrometer was employed for mass spectral analyses. Infrared spectra were determined on a Perkin-Elmer model 457 spectrophotometer. Elemental analyses were performed by Galbraith Laboratories, Knoxville, Tenn. Starting materials not described in the Experimental Section have been reported elsewhere.

Preparation of 1-Benzyl-1,4-dihydro-3-(2*H*)isoquinolones and 1-Benzyl-1,2,4,5-tetrahydro-(3*H*)-2-benazepin-3-ones. General Procedure.

The reaction sequence used for the preparation of 1-(*o*-nitrophenyl)-1,2,4,5-tetrahydro-(3*H*)-2-benzazepin-3-one (Ve) was that employed for synthesis of the other analogues.

A solution of 2-(*N*-pyrrolidyl)tetralone (11) (4.0 g., 0.02 mole) and *o*-nitrobenzyl bromide (6.5 g., 0.03 mole) in acetonitrile (120 ml.) was refluxed for 15 hours under a nitrogen atmosphere. Evaporation of the solvent afforded an orange oil which slowly crystallized. The residue was subsequently washed thoroughly with dry acetone and after filtration the imonium salt was obtained as a colorless high-melting solid, m.p. 208-211°. The imonium salt was then stirred at room temperature in a mixture of water (80 ml.), acetic acid (20 ml.) and chloroform (10 ml.) for 6 hours. Chloroform was added and the organic layer washed well with water before drying over magnesium sulfate. Evaporation of the solvent afforded IIe as tan crystals (3.7 g., 65%) after recrystallization from diethyl ether, m.p. 88-90°; ir (potassium bromide): 1705, 1513, 1345 cm^{-1}; nmr δ (deuteriochloroform): 2.40-2.71 (m, 2H, $CH_2C{=}O$), 2.98-3.25 (m, 2H, CH_2Ar), 3.46 (d, 1H, J = 5.8 Hz, CH_2Ph), 3.49 (d, 1H, J = 8.5 Hz, CH_2Ph), 3.78 (dd, 1H, CH, J = 5.8 and 8.5 Hz, CH), 6.50-7.95 (m, 8H, ArH).

Anal. Calcd. for $C_{17}H_{15}NO_3$: C, 72.58; H, 5.38. Found: C, 72.36; H, 5.41.

Compound IIe (2.81 g., 0.01 mole), hydroxylamine hydrochloride (1.1 g., 15 mmole) and sodium acetate (1.64 g., 0.02 mole) were refluxed in a solution of ethanol (10 ml.) and water (5 ml.) for 2 hours. After cooling, the solution was filtered and the filtrate extracted with chloroform. The combined extracts were washed with water before drying over sodium sulfate. Removal of the solvent left a residue which recrystallized from diethyl ether to afford .28 g. (95%) of IIIe as light yellow crystals, m.p. 161-164°; ir (potassium bromide): 3600-3000, 1608, 1515, 1350, 960 cm^{-1}; nmr δ (deuteriochloroform): 2.50-3.10 (m, 4H, CH_2-CH_2), 3.31 (d, 1H, J = 6.7 Hz, CH_2Ph), 3.33 (d, 1H, J = 8.9 Hz, CH_2Ph), 3.84 (dd, 1H-J = 6.7 and 8.9 Hz, CH), 6.70-7.92 (m, 8H, ArH).

Compound IIIe (1.0 g., 3.4 mmoles) was dissolved in chloroform (20 ml.) and cooled to -50° using a dry ice-acetone bath. With stirring, phosphorus pentachloride (0.71 g., 3.4 mmoles) was added portionwise over a period of 10 minutes so as to maintain the temperature below -30°. The mixture was stirred at -30° until all of the phosphorus pentachloride had dissolved. The temperature was then allowed to rise to room temperature and stirring was continued for 2 hours. The mixture was poured, with stirring, into water and extracted with chloroform. The combined extracts were washed with water, 5% sodium hydroxide solution and aqueous sodium chloride solution before drying over magnesium sulfate. Removal of the solvent afforded a residue which crystallized on standing. Washing of the residue with cold diethyl ether followed by recrystallization from benzene-methanol furnished 0.93 g. (93%) of Ve as colorless crystals, m.p. 214-216°; ir (potassium bromide): 3200, 1633, 1520, 1345 cm^{-1}; nmr δ (deuteriochloroform): 2.63-2.86 (m, 2H, $CH_2C{=}O$), 3.04-3.26 (m, 2H, CH_2Ar), 3.52 (d, 1H, J = 6.4 Hz, CH_2Ph), 3.54 (d, 1H, J = 8.4 Hz, CH_2Ph), 4.88 (ddd, 1H, J = 6.0, 6.4 and 8.4 Hz, CH), 6.34 (d, 1H, J = 6.0 Hz, NH), 7.20-8.10 (m, 8H, ArH); ms: m/e (relative intensity) 296 (100), 233 (18), 161 (20), 160 (60), 130 (25), 128 (20), 117 (70), 115 (53), 103 (18), 91 (30), 89 (30), 77 (25).

Anal. Calcd. for $C_{17}H_{16}N_2O_3$: C, 68.90; H, 5.44. Found: C, 69.01; H, 5.50.

Compound Va was prepared in 37% yield by the method described above. Recrystallization from benzene-hexane gave white crystals, m.p. 161-163°; ir (potassium bromide): 3320, 1665, 1600, 737, 705 cm^{-1}; nmr δ (deuteriochloroform): 2.90 (d, 1H, J = 20.0 Hz, $CH_2C{=}O$), 2.92 (dd, 1H, J = 6.0 and 13.0 Hz, CH_2Ph), 3.12 (dd, 1H, J = 5.0 and 13.0 Hz, CH_2Ph), 3.27 (d, 1H, J = 20.0 Hz, $CH_2C{=}O$), 4.80 (ddd, 1H, J = 5.0, 5.0 and 6.0 Hz, CH), 6.86-7.76 (m, 10H, ArH, NH); ms: m/e (relative intensity) 237 (.6), 147 (28), 146 (100), 118 (33), 117 (31), 91 (32), 90 (11), 65 (11).

Anal. Calcd. for $C_{16}H_{15}NO$: C, 80.98; H, 6.37. Found: C, 80.93; H, 6.45.

Compound Vc was prepared in 84% yield by the above method. Recrystallization from benzene furnished colorless crystals, m.p. 153-155°; ir (potassium bromide): 3370, 1638, 1382, 755, 705 cm^{-1}; nmr δ (deuteriochloroform): 2.54-3.57 (m, 6H, CH_2), 4.86 (ddd, 1H, J = 4.3, 5.4 and 9.5 Hz, CH), 6.10 (broad d, 1H, J = 4.3 Hz, NH), 7.25 (s, 9H, ArH); ms: m/e (relative intensity) 251 (7), 161 (27), 160 (83), 130 (20), 118 (48), 117 (100), 115 (33), 103 (10), 91 (52), 77 (15), 65 (17), 51 (8), 44 (13), 39 (10).

Anal. Calcd. for $C_{17}H_{17}NO$: C, 81.24; H, 6.82. Found: C, 81.08; H, 6.72.

A mixture of compounds Vd and VId was produced in a ratio of 1.78:1, respectively, in 58% yield, m.p. 193-214°; ir (potassium bromide): 3275, 1642, 1600, 1512, 1342, 1110, 810, 755 cm^{-1}; nmr δ (deuteriochloroform): 2.50-4.00 (m, 6H, CH_2), 4.35 (dd, .36H, J = 6.0 and 8.4 Hz, CH of VId), 4.83 (ddd, 64H, J = 4.7, 6.5 and 8.5 Hz, CH of Vd), 5.91 (broad, .36H, NH of VId), 6.47 (broad d, .64H, NH of Vd), 7.0-8.3 (m, 8H, ArH).

Anal. Calcd. for $C_{17}H_{16}N_2O_3$: C, 68.90; H, 5.44. Found: C, 68.73; H, 5.40 (mixture of Vd and VId).

Attempts to separate the individual components of this mixture were unsuccessful as the R_f values are nearly identical.

REFERENCES AND NOTES

(1) To whom inquires should be sent.

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examined in this study was highly dependant on the Lewis acid catalyst and conditions which were employed. Typically, hot concentrated sulfuric acid or polyphosphoric acid lead to ring-opened products with little or no lactam formation. Hot trifluoroacetic acid afforded only products resulting from a Semmler-Wolff aromatization reaction. Optimum conditions for lactam preparation were achieved through the use of phosphorus pentachloride in chloroform at dry ice-acetone bath temperatures.

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