Cyclic Lactams. The Hexahydrodibenzazepinones from 1,2,3,4,4a,9,10,10a-(*trans*-4a,10a)-Octahydro-9-oxophenanthrene

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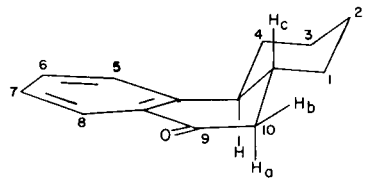
In connection with other work in this laboratory (2), we had prepared 1,2,3,4,4a,9,10,10a-(*trans*-4a,10a)-octahydro-9-oxophenanthrene (**1**) (3). This ketone offered the opportunity for preparation of two azepinones, 7a,8,9,10,11,11a-hexahydro-(*trans*-7a,11a)-5*H*-dibenz[*b*,*d*]-7*H*-azepin-6-one (**2**) and 7a,8,9,10,11,11a-hexahydro-(*trans*-7a,11a)-7*H*-dibenz[*c*,*e*]-6*H*-azepin-5-one (**3**). We have found routes to each of these cyclic lactams. The Beckmann rearrangement of the oxime tosylate of **1** afforded the lactam **2**, at the same time confirming the geometry of the oxime of ketone **1**. Schmidt rearrangement afforded a successful route to **3**, albeit in low yield.



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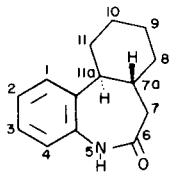

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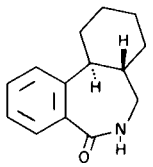

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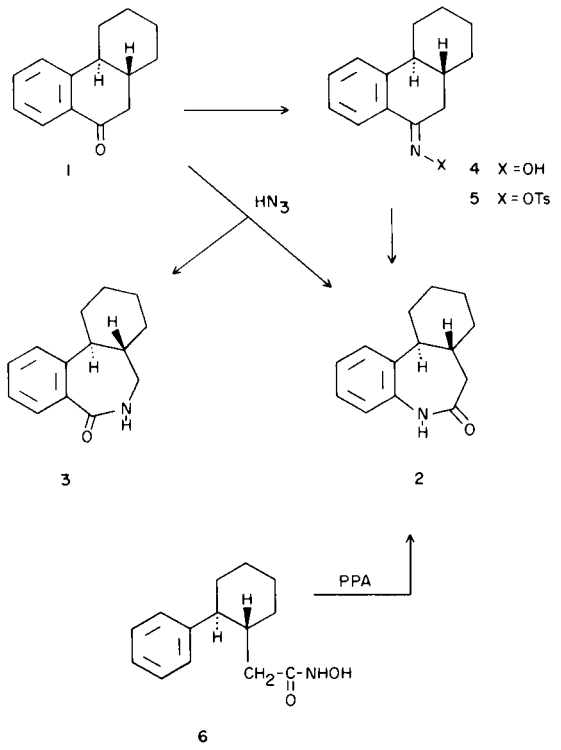
The stereochemistry of oxime **4** was tentatively assigned the *anti* geometry based on a comparison of the nmr spectrum of ketone **1**, the oxime, and the corresponding *O*-tosylate **5**. The spectrum of **1** showed a doublet of doublets for each of the protons on the α-carbon (H_a and H_b) at δ 2.23 and 2.63 (in pyridine) (4) for the axial and equatorial protons, respectively. Apparent coupling constants were J_{ab} = -17 Hz, J_{bc} = 4 Hz, and J_{ac} = 12 Hz which are consistent with the normal half-chair conformation. Deuterium exchange confirmed the assignment of the position of these signals and the coupling constants.

Oxime **4** and its tosylate, **5**, showed a doublet of doublets at δ 3.23 and 3.18, respectively, for equatorial proton H_b (5). Apparent coupling constants were J_{ab} = -17.9 Hz, and J_{bc} = 4 Hz. The signal of the axial proton, H_a, was obscured by the methylene-methine envelope in these spectra, which occurred upfield from δ 2.4. The large downfield shift of proton H_b in the oxime (*ca.* 0.6 ppm) is expected as this proton is very near the C=N bond of the oxime. Similar downfield shifts or protons α to aldoximes, and to oxime-*O*-methyl ethers have been reported (6,7). The difference in chemical shifts of protons H_a and H_b in the oxime also is evidence to support assignment of *anti* geometry to **4**. This difference (more than 1 ppm) (5) is similar to, although not as large as those observed by Trager and Huitric (8) for protons *syn* to the hydroxyl group in 4-*t*-butylcyclohexanone oxime. In chloroform, the difference in chemical shifts for the equatorial proton *syn* to the oxime is 1.68 ppm downfield, and *anti*, 0.43 ppm downfield, when compared to the ketone.

The Beckmann rearrangement of the oxime-*O*-tosylate **5** utilizing the method of Craig and Naik (9) afforded **2**. The amide which was isolated showed ultraviolet absorption at 240 mμ (ethanol), similar to that of acetanilide (10). Azepinone **2** was also prepared from *trans*-2-phenylcyclohexaneacetic acid, by conversion to the ethyl ester, treatment with hydroxylamine, followed by ring closure of the hydroxamic acid **6** with polyphosphoric acid according to the method of Wassmundt and Padegimas (12).

The Schmidt rearrangement of **1** afforded a successful route to **3**. Although the product of the reaction on α-tetralone had been previously characterized as exclusively the one from aryl rearrangement (13,14), we attempted this rearrangement on ketone **1** to determine if this analogy was applicable to our case. Uyeo (14) had previously reported alkyl rearrangement only in certain 5-methoxy, and 5,6-methylenedioxytetralones, and only the aryl group

migrated in the unsubstituted case. Careful chromatography of the reaction mixture afforded a 95% yield of **2**; however, in addition, a small amount of azepinone **3** (1.9% yield) was isolated and characterized.



Besides exhibiting typical amide carbonyl bands, the nmr spectrum was consistent with **3**. A multiplet at δ 3.25 for a single proton was observed and a quartet at δ 2.79 (J = 15 and 6.5 Hz) superimposed over the broad adsorption of the benzylic proton was observed. Exchange of the amide proton reduced this latter signal to a doublet, $J_{7,7'}$ = -15 Hz, and the former multiplet to a doublet ($J_{7,7'}$ = -15 Hz) which was broadened by further coupling with the proton at 7a. This is consistent with expected magnetic non-equivalence for the methylene protons at C-7. However, a preferred conformation could not be assigned, based on these data since more than a single conformation is consistent with these results.

EXPERIMENTAL (15)

1,2,3,4,4a,9,10,10a-(*trans*-4a,10a)-Octahydro-9-oxophenanthrene (**1**).

This ketone was prepared from *trans*-2-phenylcyclohexaneacetic acid according to the method of Gutsche and Johnson (2) in 88% yield, m.p. 95° (lit. m.p. 95-96°) (2). Deuterium exchange was accomplished in a dioxane-deuterium oxide solution with a catalytic amount of sodium ethoxide added.

1,2,3,4,4a,9,10,10a-(*trans*-4a,10a)-Octahydro-9-oxophenanthrene Oxime (**4**).

Utilizing the method of Drefahl and Martin (16), and increasing the amount of hydroxylamine hydrochloride to two equivalents, **2** was obtained in 88% yield, m.p. 176° (lit. m.p. 178°) (16). Ultraviolet spectra, λ max (95% ethanol) 253 mμ (ε = 11,200); infrared (potassium bromide), 3.05 (broad), 3.39, 3.48, 6.70, 6.85, 7.52, 7.87, 10.38, 10.61, 13.20 μ; nmr (pyridine) δ 3.23 (quartet, J_{ab} = -17.9 Hz, J_{bc} = 4 Hz, proton H_b), 1.0-2.9 (broad envelope, methine and methylene protons).

1,2,3,4,4a,9,10,10a-(*trans*-4a,10a)-Octahydro-9-oxophenanthrene Oxime-*O*-tosylate (**5**).

The *O*-tosylate, **5**, was prepared in 89% yield by the method of Drefahl and Martin (16), m.p. 177° (lit. m.p. 174.5°) (16), λ max (95% ethanol) 255 mμ (ε = 13,600); infrared (potassium bromide) 3.40, 3.48, 7.30, 8.42, 9.15, 11.90 (broad), 12.81, 13.13, 13.85, 14.00, 15.05 μ; nmr (pyridine) δ 3.18 (quartet, J_{ab} = -19 Hz, J_{bc} = 4 Hz, equatorial proton H_b), 2.24 (singlet, 4′-CH_3 protons), 0.9-2.5 (broad envelope, methylene-methine protons).

trans-2-Phenylcyclohexaneacetohydroxamic acid (**6**).

A mixture of 3.0 g. (14 mmoles) of *trans*-2-phenylcyclohexaneacetic acid (17), 3 ml. of absolute ethanol, 15 ml. of benzene, and 2 drops of sulfuric acid was refluxed for 15 hours. The mixture was then poured into a saturated aqueous solution of sodium bicarbonate and the layers partitioned. The aqueous layer was extracted with an additional portion of benzene and the organic layers were combined, washed with water, dried (sodium sulfate) and evaporated *in vacuo* to afford 3.25 g. (94%) of a colorless oil; infrared (neat), 3.40, 3.49, 5.89, 8.67, 13.24, 14.3 μ; nmr (deuteriochloroform), δ 7.18 (singlet, 5 aromatic protons), 3.94 (quartet, J = 7 Hz, -OCH_2-), 1.07 (triplet, J = 7 Hz, C-CH_3), 0.8-2.5 (envelope, methylene-methine protons).

The crude ester was allowed to react with hydroxylamine according to the method of Hauser and Renfrow (18,19). From 3.25 g. (13 mmoles) of crude ester a yield of 2.40 g. (78%) of hydroxamic acid, **6**, m.p. 157-159°, was obtained. Recrystallization from methanol-ether-hexane gave an analytical sample, m.p. 161-162°, infrared (potassium bromide), 3.12 (broad), 3.29, 3.42, 3.49, 6.21, 9.68, 10.21, 13.30, 14.32 μ; nmr (deuteriochloroform), δ 10.80 (singlet, NH and OH), 7.19 (singlet, 5 aromatic protons), 0.7-2.7 (methylene-methine envelope).

Anal. Calcd. for $C_{14}H_{19}NO_2$: C, 72.07; H, 8.21; N, 6.00. Found: C, 71.88; H, 8.19; N, 5.93.

7a,8,9,10,11,11a-Hexahydro-(*trans*-4a,10a)-5*H*-dibenz[*b*,*d*]-7*H*-azepin-6-one (**2**).

A. Beckmann Rearrangement of **5**.

Using the method of Craig and Naik (9), 1.0 g. (2.6 mmoles) of oxime-*O*-tosylate was dissolved in benzene and adsorbed on a 30 g. column of basic aluminum oxide, Brockman Activity I (Brinkman), and eluted with benzene and mixtures of benzene and increasing portions of moist chloroform. The combined fractions afforded 320 mg. (57%) of the desired cyclic amide, m.p. 187°; infrared (potassium bromide), 3.10, 3.23, 3.39, 3.48, 6.02, 6.75, 7.00, 7.22, 7.45, 7.65, 8.00, 13.30 μ; λ max (ethanol), 240 mμ (ε = 10,200); nmr (deuteriochloroform), δ 10.47 (singlet, amide NH), 7.24 (multiplet, 4 aromatic protons) 1.0-3.0 (methylene-methine envelope).

Anal. Calcd. for $C_{14}H_{17}NO$: C, 78.10; H, 7.95; N, 6.50. Found: C, 77.85; H, 8.05; N, 6.59.

B. Cyclization of **6**.

A solution of 1.0 g. (4.5 mmoles) of hydroxamic acid (**6**) in 50 g. of 115% polyphosphoric acid (FMC) was heated at 170° for 1 hour according to the method of Wassmundt and Padegimas (12). The mixture was then poured into water-ice and extracted several times with ether. The ether layers were combined, dried (sodium sulfate), and evaporated *in vacuo* affording 855 mg. of a yellow solid, m.p. 166-175°. Recrystallization from ligroine (Eastman, b.p. 63-75°) afforded yellow crystals, m.p. 170-175°. Chromatography on a dry silica gel column (20) using chloroform as eluent afforded a slightly tan solid, m.p. 184°. An additional recrystallization afforded **2**, identical in spectral data with the rearrangement product.

7a,8,9,10,11,11a-Hexahydro-(*trans*-4a,10a)-7*H*-dibenz[*c*,*e*]-6*H*-azepin-5-one (**3**).

A solution of 0.65 g. (10 mmoles) of sodium azide, 1.00 g. (5 mmoles) of **1**, and 23 g. of trichloroacetic acid was stirred for 3 hours at 60-62°. Ice water was added, the solution was made alkaline with concentrated aqueous ammonia, and the mixture was extracted with portions of chloroform. The chloroform extracts were combined, dried (magnesium sulfate), and evaporated affording 1.1 g. of an orange oil, which crystallized on standing overnight. Column chromatography on 60 g. of silica gel (Brinkmann), Brockman activity III, using chloroform as eluent afforded no material in the first 300 ml. The next 30 ml. fraction afforded 28 mg. of unidentified material, followed by 1.02 g. (95% yield) of azepinone **2** in the next 140 ml. In the next 50 ml. of chloroform eluted, 20 mg. (1.9% yield) of azepinone **3** was obtained. Recrystallization from ligroine (Eastman, b.p. 63-75°) afforded 14 mg. of colorless crystalline **4**, m.p. 180°; λ max (ethanol) 246 (ϵ = 6,300), 271 mμ (ϵ = 4,900); infrared (potassium bromide), 3.22 (broad), 3.40, 3.46, 6.04, 6.22, 6.88, 7.18, 7.40 (broad), 8.60, 10.30, 12.40, 12.65, 13.12 μ; nmr (deuteriochloroform), δ 7.10-7.90 (multiplet, 4 aromatic protons, and amide N-H), 3.24 (broad multiplet, 1 methylene proton at C-7), 2.6 (broad multiplet, 1 benzylic proton), 2.79 (quartet, 1 methylene proton, coupling constants of 15 and 6.5 Hz), 1.0-2.2 (broad envelope, methylene-methine protons). Exchange with deuterium oxide caused the multiplet at δ 3.24 to sharpen into a broadened doublet, $J_{7,7'}$ = -15 Hz, and the quartet at 2.79 to become a doublet, $J_{7,7'}$ = -15 Hz.

Anal. Calcd. for $C_{14}H_{17}NO$: C, 78.10; H, 7.95; N, 6.50. Found: C, 77.93; H, 8.05; N, 6.74.

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