Total Synthesis of a B-Ring "Homoalkaloid". 4,5,6,7,7a,8-Hexahydro-7-methylphenanthro[10,1-*bc*]azepine

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The synthesis of a novel benzazepine, 4,5,6,7,7a,8-hexahydro-7-methylphenanthro[10,1-*bc*]-azepine, is described. Two pathways leading from 1,2,4,5-tetrahydro-1-(*o*-nitrophenyl)-3*H*-2-benzazepin-3-one were investigated. The most successful route, utilizing a Pschorr cyclization followed by diborane reduction and Eschweiler-Clarke methylation, led to an excellent yield of the title compound.

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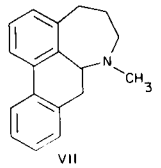
Recent years have witnessed the isolation, identification, and biological testing of several new benzazepine alkaloids. For example, cephalotaxine was first isolated and characterized by Paudler, *et al.* (3) and, later, simple esters of cephalotaxine, the harringtonines, were shown to be active against L-1210 and P-388 leukemias in mice. In addition, the rhoedanes (4) and the analogous indole alkaloid andragenine (5) have been the subject of total synthesis and biosynthetic studies, respectively. A comparison of the aporphine-like skeleton of these compounds is equally intriguing since simple aporphines, proaporphines and homoaporphines generally lack anticancer properties. Yet even among these taxonomically related compounds the cytotoxic and antileukemic homoalkaloid colchicine (6) can be found.

As part of a continuing interest in the synthesis of new and promising homoalkaloids for the treatment of cancer (7-9), a synthetic route was developed for the preparation of a B-ring homoaporphine "homoalkaloid" VII. This system incorporates the seven-membered nitrogen containing benzazepine ring found in the newest members of the homoalkaloid family but differs from "normal" homoaporphines in the site of ring enlargement. By the preparation of such a compounds, it will be possible to probe the structure-activity requirements of homoalkaloids for cancer-inhibitory activity among benzylisoquinoline alkaloids and related synthetic compounds.

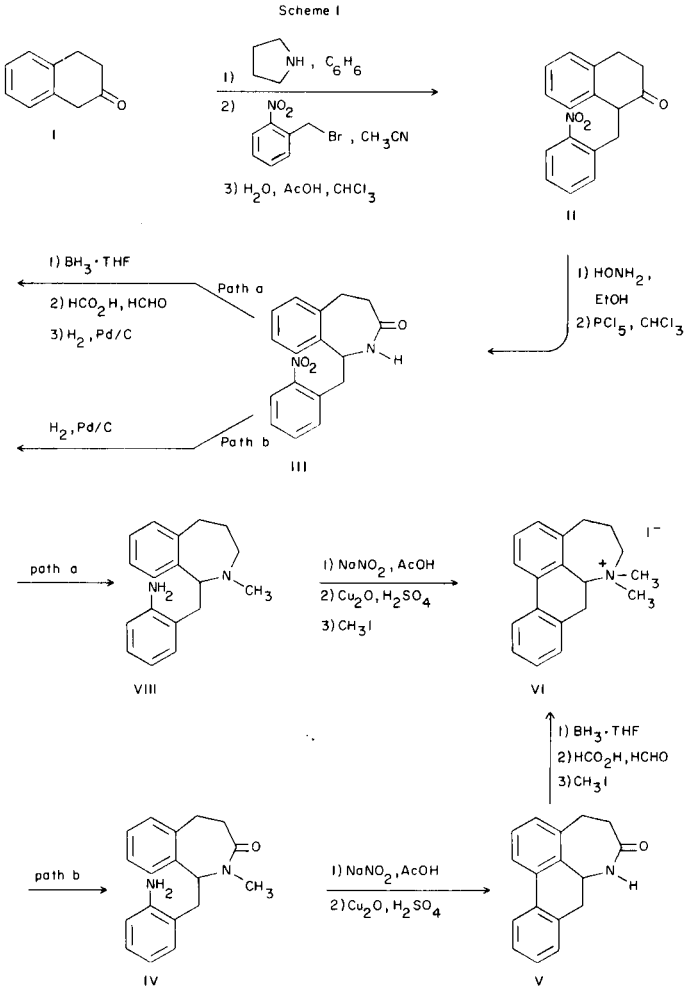


VII

Furthermore, it is extremely important that this route be amenable to reasonably large scale preparations so that animal testing of the final product can be performed. The synthetic route described in this paper is shown in Scheme I.

At the onset of this project, the use of a Pschorr cyclization was envisioned as a method for construction of the strategic bond linking A-D rings. However, Pschorr closures are generally known for their capriciousness in the preparation of isoquinoline alkaolids (10) and other polyaromatic systems (11). To mitigate this potential problem 1,2,4,5-tetrahydro-1-(*o*-nitrophenyl)-3*H*-2-benzazepin-3-one (III) was used as a pivotal compound in the synthesis of VII. From this compound two pathways could be explored which would lead to the same final product. While the two routes utilize identical chemistry, the position of

Scheme I



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the intramolecular Pschorr reaction allows for examination of the success of the cyclization when the two aromatic rings are situated differently relative to one another because of the oxidation state of the nitrogen atom in the B-ring. It was reasoned that the carbons which are to be linked would be much closer together in the amino lactam IV than in the tertiary amine VIII since ring coplanarity is induced by the amide bond. Molecular models of IV and VIII supported this contention. In order to test this hypothesis, the *o*-nitrophenylbenzazepinone III was prepared by an improved enamine alkylation reaction (8) followed by a sterically controlled Beckmann rearrangement procedure (7) developed in this laboratory.

From the beginning, path *a* proved extremely troublesome. All of the reactions yielded non-crystalline products which resisted satisfactory analyses and/or spectral interpretation. Most discouragingly, the Pschorr cyclization of the tertiary amine VIII gave only 10% of the desired product VII, also as an oil. Reaction of crude VII with methyl iodide in refluxing methanol furnished the methyl iodide salt VI as a crystalline material having proper elemental analyses. However, the overall yield of VII from 2-tetralone (I) was only 1.5%.

In contrast, path b generally provided crystalline products having excellent elemental and spectral data. Of particular importance was the isolation, purification, and identification of Pschorr-cyclized lactam V. This crystalline solid was formed in 78% yield from the aminolactam IV. Reduction of the amide carbonyl with diborane in refluxing tetrahydrofuran followed by Eschweiler-Clarke methylation provided VII as a solid in 17% overall yield based on I. Conversion of VII to VI furnished crystals which had spectral and physical characteristics identical to those of VI prepared *via* path *a*. A mixture melting point of the two materials prepared by path a and path *b* was undepressed.

Based on the considerations mentioned above, it is clear that a convenient relatively high-yielding synthetic route has been developed for the preparation of the title compound. It is of interest to compare this route with another scheme developed by Berney and Schuh (12) which led to the isolation and characterization of VII as its naphthalene-1,5-disulfonate salt. These authors, utilizing benzylated 2-tetralones, formed the benzazepine ring system *via* Schmidt reaction. However, the yields were substantially lower (*i.e.* 25-47%) than the Beckmann rearrangement route developed in these laboratories. Furthermore, while the phenanthro [10,1-*bc*]azepine VII was synthesized by both groups using a modified Pschorr reaction, the methodology described in this paper leads to the isolation and characterization of VII as the pure crystalline free-base in 78% yield while the route of Berney and Schuh furnished only 24% of VII as a salt derivative. A majority of the product from their reaction proved to be a phenolic non-cyclized material.

EXPERIMENTAL

Melting points were obtained with a Thomas-Hoover melting point apparatus and are 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. A DuPont model 21-491 mass spectrometer was employed for mass spectral analyses. Infrared spectra were determined on a Perkin-Elmer model 457 spectrophotometer. Ultraviolet spectra were taken on a Carey 14 recording spectrophotometer. Elemental analyses were performed by Galbraith Laboratories, Knoxville, Tenn.

2-Tetralone (I).

This compound was prepared by the method of Stoffer and co-workers (13), b.p. 77° (0.3 mm); lit. b.p. 70-71° (0.25 mm).

1-(*o*-Nitrophenyl)-2-tetralone (II).

Compound II was prepared in 65% yield by an improved enamine alkylation reaction described in a previous paper (7), m.p. 108-110°; lit. m.p. 108-110°.

1,2,4,5-Tetrahydro-1-(*o*-nitrophenyl)-3*H*-2-benzazepine-3-one (III).

This material was obtained in 93% yield by a Beckman rearrangement reaction described in a previous publication (7), m.p. 214-216°; lit. m.p. 214-216°.

4,5,7a,8-Tetrahydrophenanthro[10,1-*bc*]azepin-6-(7*H*)one (V).

The nitrolactam III (4.0 g., 13.4 mmoles) was dissolved in a mixture of ethanol (100 ml.) and acetic acid (25 ml.) containing palladium on powdered charcoal (0.5 g., 4%). Hydrogenation was carried out at 30 psi for 8 hours. The catalyst was removed by filtration through Celite and the solvent was then evaporated to afford IV (3.3 g., 94%). Because of the extreme sensitivity of this subtance to oxygen it was used without further purification for subsequent transformation.

Under nitrogen, the aminolactam IV (1.85 g., 6.7 mmoles) was dissolved in acetic acid (90 ml.) and cooled to 0°. Sodium nitrite (0.68 g., 9.4 mmoles) in water (40 ml.) was added dropwise to the acetic acid solution over a period of 0.5 hours. After stirring for 1 hour at 0°, sulfamic acid (0.34 g., 33.5 mmoles) was added in one portion. This solution, in turn, was added, under nitrogen, to cuprous oxide (2.55 g., 26.8 mmoles) in concentrated sulfuric acid (15 ml.) at 0° over 0.5 hours. The mixture was allowed to warm to room temperature and then stirred for an additional 15 hours. The solution was filtered and made alkaline with aqueous ammonia before extracting with methylene chloride. The combined extracts were washed with dilute aqueous sodium sulfate. Removal of the solvent *in vacuo* followed by washings of the filter cake with ether furnished V as an off-white powder (1.35 g., 78%). m.p. 207-209°. Recrystallization from benzene produced white needles, m.p. 213°; ir (chloroform): 3400, 3010, 2950, 1660, 1635, 1450 cm^{-1}; nmr (deuteriochloroform): δ 2.30-3.40 (m, 6H, CH_2-CH_2 and CH_2), 4.90 (dt, 1H, ArCHN), 6.60 (b, 1H, NH), 7.10-7.80 (m, 7H, ArH); uv (ethanol): λ max 270 nm; ms: m/e (relative intensity) 249 (90), 231 (15), 218 (25), 204 (67), 203 (75), 191 (100), 178 (34), 165 (23).

Anal. Calcd. for $C_{17}H_{15}NO$: C, 81.91; H, 6.06; N, 5.67. Found: C, 82.00; H, 6.12; N, 5.67.

4,5,6,7,7a,8-Hexahydro-7-methylphenanthro[10,1-*bc*]azepine (VII).

The lactam V (0.47 g., 1.9 mmoles) was suspended in dry tetrahydrofuran (25 ml.) under a nitrogen atmosphere. Diborane in tetrahydrofuran (2 ml., 1*M*) was added slowly over a period of 15 minutes and stirred at room temperature for 0.5 hours. The solution was then heated at reflux for 15 hours. After cooling, dilute hydrochloric acid (5 ml. 2*M*) and water (5 ml.) were added. Following a reflux period of 0.5

hours, the solution was neutralized with dilute sodium bicarbonate solution before extracting with ether. The combined extracts were washed with dilute sodium bicarbonate, water, and saturated sodium chloride solution. After drying over sodium sulfate, the solvent was removed yielding the cyclic secondary amine (0.39 g., 88%).

The secondary amine (0.29 g., 1.23 mmoles) was immediately dissolved in formaldehyde solution (10 ml., 40%) and formic acid (20 ml.). After stirring for 18 hours, water (25 ml.) was added and the reaction mixture made alkaline with dilute sodium hydroxide solution. The mixture was then extracted with methylene chloride. The combined extracts were washed with dilute sodium bisulfite, dilute sodium bicarbonate, water, and saturated sodium chloride solution before drying over magnesium sulfate. The solvent was removed *in vacuo* and the residue distilled to afford VII as a colorless oil (0.15 g., 49%), b.p. 170° (0.10 mm), which slowly crystallized upon standing, affording a wax-like material; ir (film): 3035, 2937, 1587, 1480, 1060, 952 cm^{-1}; nmr (deuteriochloroform): δ 1.80 (s, 3H, NCH_3), 1.1-3.5 (m, 8H, CH_2), 4.85 (dd, 1H, ArCHN), 6.8-7.9 (m, 7H, ArH); ms: m/e (relative intensity) 249 (100), 248 (67), 234 (43), 220 (26), 204 (95), 191 (87), 178 (37), 165 (27), 153 (15).

Anal. Calcd. for $C_{18}H_{19}N$: C, 86.70; H, 7.68; N, 5.61. Found: C, 86.53; H, 7.93; N, 5.49.

4,5,6,7,7a,8-Hexahydro-7-methylphenanthro[10,1-*bc*]azepine Methiodide (VI).

The methyl iodide salt VI was prepared in a refluxing methanol solution of VII and methyl iodide. Evaporation of the solvent afforded a brown residue which recrystallized from methanol-ether to afford white crystals, m.p. 177-178°. The methyl iodide derivative of VII prepared by path a melted at 176-177°. A mixture melting point of these two materials was undepressed, m.p. 176-178°; nmr (DMSO-d_6): 2.0-4.1 (m, 8H, CH_2), 3.30 (s, 6H, $2NCH_3$), 5.20 (b, 1H, ArCH), 7.1-8.1 (m, 7H, ArH); ms: m/e (relative intensity) 263 (63), 218 (13), 217 (11), 215 (13), 204 (32), 203 (59), 202 (49), 192 (45), 191 (49), 189 (57), 178 (20), 176 (26), 165 (27), 128 (100).

Anal. Calcd. for $C_{19}H_{22}IN$: C, 58.31; H, 5.66; N, 3.59. Found: C, 58.21; H, 5.80; N, 3.44.

REFERENCES AND NOTES

(1) To whom inquires should be sent.

(2a) Taken, in part, from a thesis by M. A. Woods in partial fulfillment of the requirements for the M. S. degree in organic chemistry, University of Maine at Orono, Orono, Maine 04473; (b) A preliminary account of this work was presented, in part, at the 8th Northeast Regional Meeting of the American Chemical Society, Boston, Mass., June 1978, Abstract No. 53.

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