

The Synthesis of *syn*- and *anti*-11-Hydroxy-12-methyl-10,11-dihydro-5,10-imino[5*H*]dibenzo[*a,d*]cycloheptene

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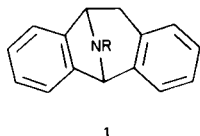
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The synthesis of *anti*-11-hydroxy-12-methyl-10,11-dihydro-5,10-imino[5*H*]dibenzo[*a,d*]cycloheptene (**3**) is reported. The assigned structure of **3**, was confirmed by comparison of the infrared and nmr spectra of **3** with that of the *syn*-11-hydroxy derivative, **8**, prepared from **3** via a series of transformations. Key features in the synthesis include cyclization of an unsaturated amine to an azatetracyclic halide and solvolysis via an aziridinium ion to give **3**.

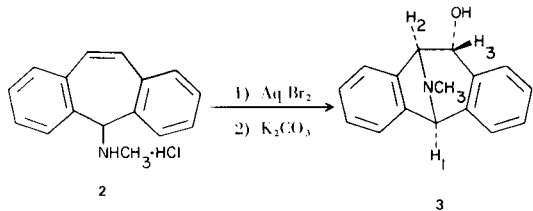
J. Heterocyclic Chem., **13**, 1355 (1976).

Sir:

A recent report by Frechet and Nedelec (1) on the synthesis of the novel dibenzocycloheptene ring system **1** prompts us to report our work on closely related structures.



Treatment of an aqueous solution of the amine hydrochloride, **2** (**2**), with aqueous bromine (1 equivalent) followed immediately by basification with potassium carbonate and dilution with THF gave compound **3** as the major amine product after stirring the reaction mixture overnight at room temperature.

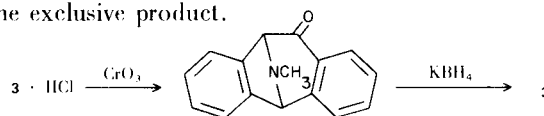


Compound **3** was isolated from the reaction mixture by the following procedure. The crude mixture was extracted with dichloromethane and the organic phase was back extracted with dilute hydrochloric acid. The acid phase was made basic with potassium hydroxide and extracted with dichloromethane to give a crude mixture of amine products with compound **3** and the free base of **2** being the major products detected by thin layer

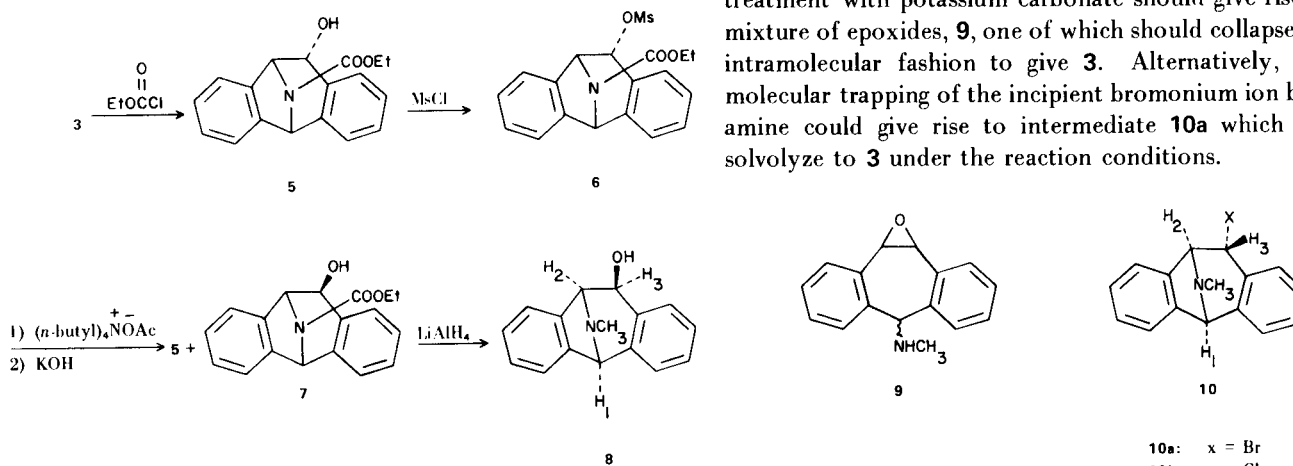
chromatography. The mixture was chromatographed on silica gel using benzene and increasing amounts of ethyl acetate as eluants to give **3** in 20% yield. Recrystallization from benzene afforded an analytical sample of **3** (**3**), m.p. 202-203°; nmr (DMSO-*d*₆): (4) δ 2.27 (s, N-CH₃), δ 4.16 (d, J = 6 Hz, H₂), δ 4.54 (s, H₁), δ 5.00 (d, J = 6 Hz, H₃); ir (0.005 *M* in carbon tetrachloride); 3595 cm⁻¹.

Examination of molecular models indicates that H₂ and H₃ of compound **3** form an angle of approximately 35° when viewed along the C₁₀-C₁₁ axis. On the contrary the angle formed by H₂ and H₃ for the epimeric *syn* alcohol is approximately 90°. Utilizing the Williamson-Johnson (5) modification of the Karplus equation one would predict a coupling constant of ~6-7 Hz for **3** and a coupling constant of ~0 Hz for the *syn* alcohol. The observed value of 6 Hz is in excellent agreement with the predicted value. The assigned structure is also supported by the infrared absorption at 3595 cm⁻¹ for a 0.005*M* solution of **3** in carbon tetrachloride which is characteristic of a free hydroxyl group. Although the spectral data were consistent for the assigned structure of **3**, the epimeric alcohol was needed to assign the stereochemistry unequivocally.

Oxidation of the hydrochloride of **3** (prepared *in situ*) with Jones reagent gave the ketone **4** as a chromatographically homogeneous yellow oil. However, an attempt to reduce **4** with aqueous potassium borohydride gave **3** as the exclusive product.



Compound **3** was successfully converted into the epimeric alcohol **8** via the following reaction sequence.



Treatment of **3** with ethyl chloroformate in refluxing benzene followed by recrystallization from dichloromethane/ether afforded **5**; m.p. 185-185.5°; nmr (deuteriochloroform): (4) δ 1.22 (t, $J = 7$ Hz, 3H), δ 4.13 (q, $J = 7$ Hz, 2H), δ 5.22 (d, $J = 6$ Hz, 1H), δ 5.50 (d, $J = 6$ Hz, 1H), δ 5.73 (s, 1H). As in the case of **3**, oxidation of **5** with Jones reagent followed by reduction with either aqueous potassium borohydride or triisobutylaluminum in toluene gave **5** as the exclusive product. Compound **5** was converted into the corresponding mesylate **6** with methanesulfonyl chloride in pyridine. Treatment of **6** with tetra-*n*-butylammonium acetate (**6**) in *N*-methylpyrrolidone at 140° for 2 hours followed by hydrolysis of the crude product with methanolic potassium hydroxide gave a mixture of **5** and **7** which were isolated in 26% and 35% yield respectively via low pressure chromatography on silica gel using benzene and ethyl acetate as eluants. Recrystallization from dichloromethane/skellysolve B gave an analytical sample of **7**, m.p. 146.5-147.5°; nmr (deuteriochloroform): (4) δ 1.20 (t, $J = 7$ Hz, 3H), δ 4.14 (q, $J = 7$ Hz, 2H), δ 4.53 (s, 1H), δ 5.57 (s, 1H), δ 5.81 (s, 1H). Reduction of **7** with lithium aluminum hydride in ether followed by chromatography on silica gel using ethanol and ethyl acetate as eluants and recrystallization from ether gave **8**, m.p. 147.5-148.5°; nmr (DMSO-d_6): (4) δ 2.33 (s, N-CH₃), δ 4.13 (s [broad], H₂), δ 4.28 (d, $J = 1$ Hz, H₃), δ 4.63 (s, H₁); ir (0.005M in carbon tetrachloride): 3560 cm^{-1} .

The observed coupling constant for H₂ and H₃ in **8** is approximately 1 Hz or less which is in excellent agreement with the predicted value. The infrared absorption at 3560 cm^{-1} , which is characteristic of an intramolecularly bonded hydroxyl group, further confirms the assigned structure of **8**.

Mechanistically one can envision two different inter-

mediates which can give rise to **3**. Initial addition of hypobromous acid to the double bond followed by treatment with potassium carbonate should give rise to a mixture of epoxides, **9**, one of which should collapse in an intramolecular fashion to give **3**. Alternatively, intramolecular trapping of the incipient bromonium ion by the amine could give rise to intermediate **10a** which could solvolyze to **3** under the reaction conditions.

When the reaction mixture was worked up after stirring with potassium carbonate for only 5 hours there was obtained in 10% yield a product whose nmr and mass spectra were consistent with that expected for a mixture of **10a** and **10b**. Protons H₂ and H₃ appeared as doublets at δ 4.35 and δ 5.62 respectively with coupling constants of 6 Hz indicating that the halogen atom was *anti* to the nitrogen bridge. The mass spectrum showed M^+/e values of 255 and 299 indicative of a mixture of chloride and bromide. Solvolysis of the halide mixture in aqueous potassium carbonate/THF resulted in a quantitative conversion to **3**. The chloride **10b** presumably arises by halide ion exchange with the initially formed bromide **10a** via the same aziridinium ion which ultimately leads to **3**.

Although the epoxide mechanism cannot be ruled out on the basis of our results, the fact that a tetracyclic halide could be isolated and converted into **3** under the reaction conditions indicates that trapping of the incipient bromonium ion by the amine is probably the major reaction pathway.

Acknowledgment.

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REFERENCES AND NOTES

- (1) D. Frechet and L. Nedelec, U. S. Patent 3892756 (1975).
- (2) F. Hoffmann-LaRoche and Co. A. G., Netherlands Application 6,600,093 (1966); *Chem. Abstr.*, **66**, 2426a (1967).
- (3) Satisfactory spectral and microanalytical data were obtained for all new compounds.
- (4) δ Values were obtained from the deuterium oxide exchange nmr spectra.
- (5) K. L. Williamson and W. S. Johnson, *J. Am. Chem. Soc.*, **83**, 4623 (1961).
- (6) For preparation of the reagent see: R. Baker, J. Hudec, K. L. Rabone, *J. Chem. Soc. (C)*, 1605 (1969).