Isoneopine from Thebaine

Ahmad Seyed-Mozaffari and Sydney Archer*

Cogswell Laboratory, Rensselaer Polytechnic Institute, Troy, New York 12181

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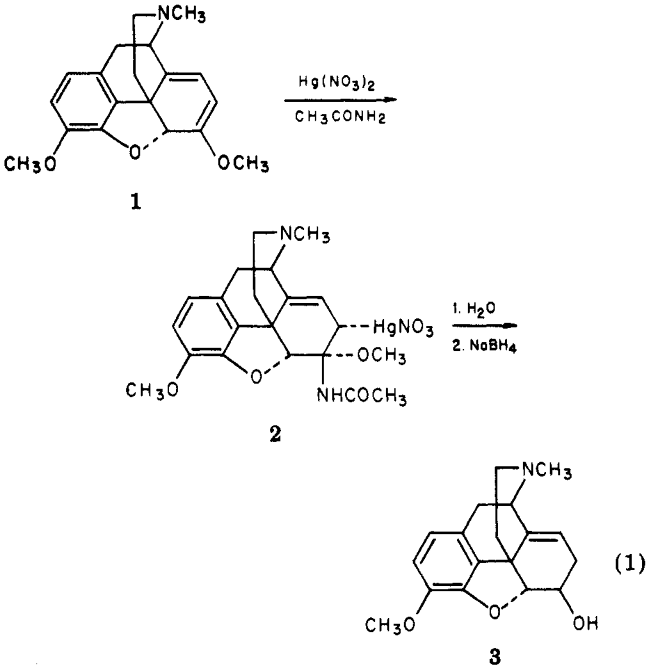
Barluenga et al.[1] reported that amidomercuration-demercuration of olefins using dry $Hg(NO_3)_2$ furnished N-substituted amides. We found that when thebaine, 1, was used as the olefinic substrate, isoneopine, 3, was obtained in 38% yield, which after one crystallization was analytically pure, and 39% of the starting material was recovered. Little, if any, neopine was detected in the reaction products. The reaction probably proceeded as shown in eq 1.



(1)

That both $Hg(NO_3)_2$ and acetamide were necessary was demonstrated by the following observations: (1) omission of the inorganic reagent resulted in almost quantitative recovery of 1, (2) omission of the amide resulted in the formation of a mixture of neopine and isoneopine in about 9% yield accompanied by a small quantity of an unidentified product. Slightly more than 61% of thebaine was recovered unchanged.

It is not surprising that 1,2 rather than 1,4 addition occurred since Barber and Rapoport[2] reported that oxymercuration of thebaine with $Hg(O_2CCH_3)_2$ in methanol afforded 7α-acetomercurineopinone dimethyl ketal.

These authors also reported that when thebaine was allowed to react with $Hg(O_2CCH_3)_2$ in methanol followed by treatment of the product with 3 N acetic acid and saturated KBr solution, crystalline neopinone was obtained in 97-100% yield.[2] Subsequently, Wunderly and Brochmann-Hensen[3] found that reduction of this material with alkaline aqueous $NaBH_4$ solution furnished, in 98% yield, a mixture of neopine and isoneopine in the ratio of 11:89.

We repeated these experiments with different results. In our hands, repetition to the Barber-Rapoport[2] experiment gave a residue in 118.0% yield. Thin-layer chromatography showed that it was a mixture of small amounts of thebaine and neopinone and a major component that was a noncrystalline mercury-containing material, clearly not neopinone. Apparently, the acid-KBr treatment did not demercurate the intermediate to any appreciable extent.

Repetition of the Wunderly-Brochmann-Hansen[3] reduction gave the crude reaction mixture in 90% rather than the reported 98%. Although our crude yield was in essential agreement with that stated, analytical chromatography revealed the presence of more components in the crude glassy residue than only the two reported. In addition to recovered thebaine, the neopine that was isolated was accompanied by a minor byproduct of unknown structure and the isoneopine was contaminated with two minor byproducts. The yield of slightly impure neopine was 21% and 67% for isoneopine of similar purity.

Experimental Section

General Methods. Melting points were determined on a Mel-temp apparatus and are corrected. NMR spectra were run either on a Varian T-60A or a Hitachi Perkin-Elmer R-600 spectrometer using Me_4Si as the internal standard. IR spectra were recorded on a Perkin-Elmer 298 spectrometer. Mass spectra were run at the Sterling-Winthrop Research Institute. We are grateful to Ms. C. Martini and Dr. S. Clemens for their cooperation. Elementary analyses were performed by Spang Microanalytical Laboratory, Eagle Harbor, MI.

Isoneopine (3). A suspension of 3.11 g (0.01 mol) of thebaine, 5.9 g (0.1 mol) of acetamide, and 3.25 g (0.01 mol) of anhydrous $Hg(NO_3)_2$ in 60 mL of dry CH_2Cl_2 was stirred under reflux under N_2 for 2 h. The mixture was cooled to 0 °C and treated with 10 mL of $(C_2H_5)_3N$ and 30 mL of 10% aqueous NaOH. A solution of 379 mg (0.01 mol) of $NaBH_4$ in 10 mL of 10% NaOH was added dropwise and stirring at 0 °C was continued for an additional 30 min. The mixture was filtered through a bed of Celite and the cake was washed with 200 mL of CH_2Cl_2 followed by 50 mL of CH_3OH. The layers were separated, and the aqueous phase was extracted with 100 mL of CH_2Cl_2. The combined organic layers were washed with H_2O and concentrated to leave 2.9 g of a brown gum, which was chromatographed on basic alumina with $CHCl_3$ as the eluant. The first fractions yielded thebaine, wt 1.2 g (39% recovery) after recrystallization from CH_3OH, mp. 193-195 °C, identical in all respects with an authentic sample.

Later fractions furnished 1.12 g (38%) of isoneopine, mp 159-161 °C, which, after recrystallization from CH_3OH-ether, melted at 163-164 °C. Okuda[4,5] report mp 153-156 °C. Our material did not depress the melting point of an authentic sample prepared by $NaBH_4$ reduction of neopinone. The IR and NMR spectra of the two samples were identical. IR (KBr) 3100 cm^{-1} (OH, br); NMR ($CDCl_3$) β 1.73-2.40 (br m, 4 H, H-7, H-15), 2.40-2.67 (m, 2 H, H-16), 2.46 (s, 3 H, NCH_3), 2.75 (d, 1 H, H-10α) 3.28 (d, 1 H, H-10β), 3.30 (br s, 1 H, H-60H, exchangeable with D_2O), 3.60 (d, 1 H, H-9α), 3.70 (br m, 1 H, 6-H), 3.89 (s, 3 H, OCH_3), 4.52 (d, 1 H, H-5β), 5.50 (t, 1 H, H-8), 6.68 (2 H aromatic H); mass spectrum, *m/e* 299 (M^+), 298 ($M^+ - 1$), 284 ($M^+ - CH_3$), 268 ($M^+ - OCH_3$). Anal. Calcd for $C_{18}H_{21}NO_3$: C, 72.22; H, 7.07; N, 4.68. Found: C, 72.08; H, 7.01% N, 4.62.

When the same reaction was carried out without the $Hg(NO_3)_2$, 2.98 g (96%) of thebaine, mp 193-194 °C, was recovered. When the acetamide was omitted, 1.9 g (61%) of thebaine was recovered. A mixture of neopine and isoneopine, wt 280 mg (9%), was also obtained in which the former was the major component.

Neopinone from Thebaine (Barber-Rapoport[2]). The described procedure was followed as closely as possible. One gram of thebaine gave 1.14 g (reported 0.995 g) of the purported neopinone. The IR spectrum (KBr) showed a small peak at 1720 cm^{-1}. TLC revealed the presence of three components. The two minor compounds were thebaine and neopinone. The major compound

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was a mercury-containing material, which, on reduction with alkaline $NaBH_4$, furnished a gray precipitate, which was probably metallic Hg.[6]

Neopine and Isoneopine (Wunderly and Brochmann-Hansen[3]). A suspension of 400 mg (1.3 mmol) of thebaine in 16 mL of CH_3OH was added to a stirred suspension of 616 mg (1.9 mmol) of Hg $(O_2CCH_3)_2$ in 12 mL of CH_3OH and the resultant mixture was heated at reflux under N_2 for 50 min. The hot suspension was filtered and the filter cake was washed with 30 mL of CH_3OH. The combined filtrates were evaporated to dryness, leaving 1.005 g of a glassy residue, which was dissolved in 40 mL of 3 N acetic acid. The solution was stirred at room temperature under N_2 for 90 min before being treated with 28 mL of saturated KBr solution. Stirring at room temperature was continued for 60 min and the mixture was filtered. The cake was washed with H_2O, and the combined filtrates were cooled to 0 °C and made strongly alkaline by cautious, portionwise addition of 8.0 g of KOH pellets. A solution of 1.0 g of $NaBH_4$ in 20 mL of H_2O was added over a period of about 5 min. When the addition was complete, the dark-gray suspension was extracted with several portions of $CHCl_3$. The combined extracts were filtered, and the filtrate was concentrated to dryness to leave a brownish, glassy solid, wt 346 mg. This material was chromatographed on 25 g f neutral alumina, using a 3:1 mixture of benzene:$CHCl_3$ for the first three fractions and a 3:2 mixture of the same solvents for the next 3 fractions. Fraction A (1 mg) was thebaine; fraction B (11 mg) was a mixture of thebaine, neopine, and a minor unidentified product; fraction C (10.5 mg) was TLC pure neopine; fraction D (59.4 mg) consisted mainly of neopine and two minor impurities; fraction E (147 mg) was isoneopine contaminated with two minor impurities; fraction F (109 mg) was isoneopine contaminated by one minor impurity. Thus, there was obtained 81 mg (21%) of slightly impure neopine and 256 mg (67%) slightly impure isoneopine. The reported yield[3] of neopine was 11% and 89% for isoneopine, without comment concerning the purity of these isomers.

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Registry No. 1, 115-37-7; 3, 16008-33-6; neopinone, 509-66-0; neopine, 467-14-1.

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[6] Dr. R. Ravichandran, a colleague of Professor A. Schultz of this laboratory, repeated this experiment with essentially the same results.

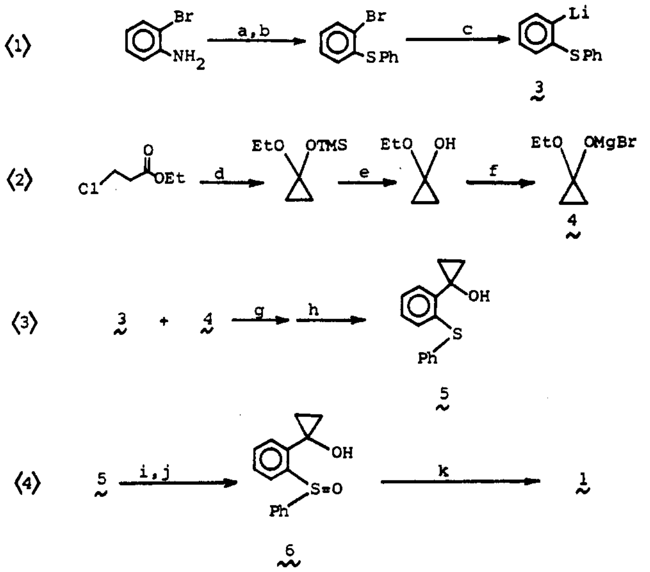
Communications

Synthesis and Reactivity of a Cyclopropyloxy Sulfurane

Summary: We have synthesized cyclopropyloxy sulfurane 1 and report its reactivity relative to *gem*-dimethyl sulfurane 2; the change in reactivity brought about by a minor alteration of the geometry of the five-membered ring is large.

Sir: Westheimer's 1956 observation[1] that barium ethylene phosphate hydrolyzes about 10^7 times faster than barium dimethyl phosphate prompted investigation of the hydrolytic behavior of five-membered cyclic phosphates,[2] phosphonates,[3] phosphonium salts,[4] sulfites,[5] and sulfates[6] vs. their respective acyclic analogues. To one extent or another, it was found that a process that converts a tetrahedral phosphorus or sulfur contained in a five-membered ring to a trigonal-bipyramidal (TBP) phosphorus or sulfur with the five-membered ring spanning axial and equatorial sites is very strongly favored over the same tetrahedral-to-TBP process in a different-sized ring or an acyclic system. The connection between this "five-membered ring effect" and sulfurane chemistry was pointed out by Martin,[7] who realized that sulfurane hydrolysis converts sulfur from TBP to tetrahedral, and therefore this process in a five-membered ring should be, and is,[8] very strongly disfavored relative to acyclic analogues. The exact origin of the five-membered ring effect is subject to various interpretations. In some cases,[9] it may be fairly argued that tetrahedral phosphorus is strained and the facility of hy-

Scheme I[a]



[a] (a) H_2SO_4, $NaNO_2$, 0 °C; (b) NaOH, Cu bronze, PhSH, 5 °C; (c) *n*-BuLi; (d) Na, Et_2O, Me_3SiCl; (e) MeOH, 2 days, room temperature; (f) MeMgBr; (g) Et_2O, reflux 24 h; (h) 0 °C, saturated aqueous NH_4Cl; (i) *t*-BuOCl; (j) 10% aqueous NaOH; (k) CH_3COCl.

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