

Sydney Archer and Peter Osei-Gyimah

Chemistry Department, Rensselaer Polytechnic Institute, Troy, New York 12181

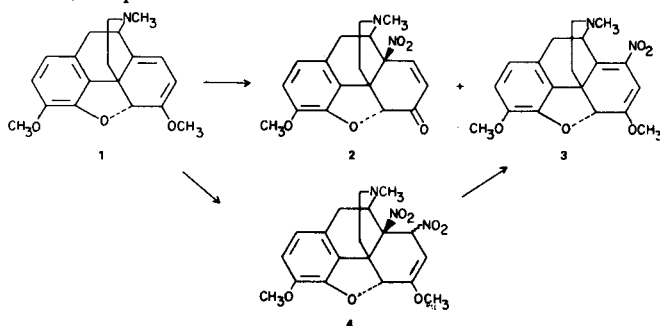
Received July 17, 1978

Treatment of thebaine with dinitrogen tetroxide gave a mixture of 14 $\beta$ -nitrocodeinone (23%) and 8-nitrothebaine (7%).

*J. Heterocyclic Chem.*, 16, 389 (1979).

14-Nitrocodeinone (**2**) was prepared by Kirby (1) in unspecified yield by treating thebaine (**1**) with tetranitromethane followed by hydrolysis of the adduct. We have found that thebaine reacts with dinitrogen tetroxide to give, after hydrolysis, the desired 14-nitrocodeinone (**2**) in 23% yield and accompanied by another mononitro compound to which we assigned structure **3**. This assignment was supported by elemental analysis, ir and nmr spectra. The most unusual feature of the latter spectrum was the downfield shift of the C-9 $\alpha$  proton doublet which appeared at  $\delta$  4.82 ( $J_{9\alpha,10\alpha} = 6$  Hz). In the case of 14-nitrocodeinone (**2**) this proton gave a signal at  $\delta$  3.6 (2). 8-Nitrothebaine (**3**) probably was formed by the 1,2-addition of dinitrogen tetroxide across the C-8 and C-14 double bond of **1** to give **4** (**3**). The acidity of the C-8 allylic proton facilitated the loss of the elements of nitrous acid, which resulted in the formation of **3**. Thus 1,2 as well as 1,4 addition to the diene system of thebaine occurred.

In this connection Brossi and co-workers (4) found that treatment of **1** with *m*-chloroperbenzoic acid in a mixture of acetic and trifluoroacetic acids as described by Carroll (5) gave in addition to 14-hydroxycodeinone, 14-hydroxy-8-acetoxydihydrothebaine which arose by epoxidation of the 8,14 double bond followed by acetylation of the 8,14 epoxide.



## EXPERIMENTAL

Melting points were taken on a Laboratory Devices Mel-Temp apparatus and were corrected. Infrared spectra were obtained on a Perkin-Elmer model 137 spectrophotometer. The nmr spectra were recorded on a Varian T-60A spectrometer with TMS as the internal standard. Chemical analyses were determined by Instranal Laboratory, Rensselaer, New York.

14-Nitrocodeinone (**2**) and 8-Nitrothebaine (**3**).

Dinitrogen tetroxide (**6**) (1.06 g., 0.012 mole) in cold, dry ethyl acetate (10 ml., flushed with nitrogen) was added within 0022-152X/79/020389-01\$02.25

15 minutes to a stirred solution of thebaine (1.8 g., 0.0059 mole) in 60 ml. of dry THF (flushed with nitrogen) maintained at  $-25^{\circ}$ .

The mixture was allowed to stir at this temperature for 15 minutes and then allowed to warm to  $-10^{\circ}$ . After 0.5 hour, the mixture was neutralized with 40 ml. of cold, saturated sodium bicarbonate solution, while keeping the system below  $0^{\circ}$ , stirred for 0.5 hour and extracted with chloroform. The chloroform extract was washed with aqueous sodium bicarbonate solution, water, dried (magnesium sulfate) and concentrated *in vacuo* to afford a brown oil which was chromatographed on a preparative tlc plate (silica gel) with ether as the eluent. 14-Nitrocodeinone (**2**), which appeared as a band at the solvent front, was removed by extraction (chloroform) to give a solid residue upon removal of the solvent. Recrystallization of the solid from ethanol yielded **2** as pale yellow crystals, 0.41 g. (23%), m.p.  $169-171^{\circ}$  (Lit. (1) m.p.  $172-173^{\circ}$ ); ir (potassium bromide):  $1695\text{ cm}^{-1}$  (C=O); nmr (deuteriochloroform):  $\delta$  6.65 (2H, aromatic), 6.58 (d, 1H,  $J = 10.5$  Hz, 7-H), 6.18 (d, 1H,  $J = 10.5$  Hz, 8-H), 5.12 (s, 1H, 5-H), 4.10 (d, 1H,  $J = 6.0$  Hz, 9-H), 3.90 (s, 3H, OCH<sub>3</sub>), 3.30 (d,  $J = 18$  Hz, 10 $\beta$ -H), 2.39 (s, 3H, NCH<sub>3</sub>).

Anal. Calcd. for C<sub>18</sub>H<sub>18</sub>N<sub>2</sub>O<sub>3</sub>: C, 63.15; H, 5.30; N, 8.18. Found: C, 63.54; H, 5.38; N, 8.00.

8-Nitrothebaine (**3**) which appeared as a middle band on the preparative tlc plate was removed to give yellow microcrystals after crystallization from ethanol (0.18 g., 7%), m.p.  $181-183^{\circ}$ ; nmr (deuteriochloroform):  $\delta$  6.70 (2H, aromatic), 5.68 (s, 1H, 7-H), 5.23 (s, 1H, 5-H), 4.82 (d, 1H,  $J = 6.0$  Hz, 9-H), 3.85 (s, 3H, O-CH<sub>3</sub>), 3.70 (s, 3H, O-CH<sub>3</sub>), 2.40 (s, 3H, NCH<sub>3</sub>).

Anal. Calcd. for C<sub>19</sub>H<sub>20</sub>N<sub>2</sub>O<sub>5</sub>: C, 64.03; H, 5.65; N, 7.86. Found: C, 64.35; H, 5.72; N, 7.88.

Acknowledgement.

This investigation was supported by a grant from the National Institute on Drug Abuse (DA-01674).

## REFERENCES AND NOTES

- (1) R. M. Allen and G. W. Dirby, *Chem. Commun.*, 1346 (1970).
- (2) S. Okuda, S. Yamaguchi, Y. Kawazoe, and K. Tsuda, *Chem. Pharm. Bull.*, 12, 104 (1964).
- (3) We are uncertain of the stereochemistry of **4** at C-8. Schecter, *et al.*, (H. Schecter, J. O. Gardikes, T. S. Cantreu and G. U. D. Tiers, *J. Am. Chem. Soc.*, 89, 3005 (1967), found that addition of dinitrogen tetroxide to  $\Delta^9,10$ octalin gave the *trans* adduct whereas addition to norbornene under conditions of near-kinetic control gave principally the *exo-cis* isomer.
- (4) I. Ikuma, K. C. Rice, and A. Brossi, *Helv. Chim. Acta*, 60, 2135 (1977).
- (5) F. M. Hauser, T-K. Chen, and F. I. Carroll, *J. Med. Chem.*, 17, 1117 (1974).
- (6) Nitrogen dioxide was distilled from a cylinder (Matheson) into a vessel protected from moisture and cooled in a Dry-Ice bath. The condensate was re-distilled into a weighing vessel and transferred to the reaction flask. The dinitrogen tetroxide obtained this way was a white crystalline solid at this temperature.

© HeteroCorporation