An Improved Synthesis of Norcocaine

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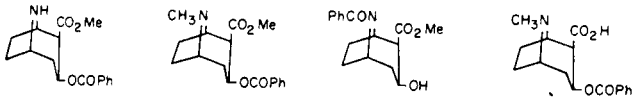
An improved, high yielding procedure for the preparation of norcocaine from cocaine is described. The synthesis is accomplished by controlling the *p*H during the potassium permanganate oxidation. A quantitative conversion of *N*-benzoylecgonine methyl ester into norcocaine by dry, hydrogen chloride-dioxane is also included.

J. Heterocyclic Chem., 13, 363 (1976).

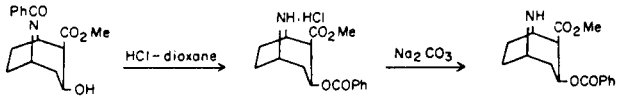
Norcocaine can now be obtained in higher yields from cocaine than was heretofore possible. Norcocaine (I), the primary photoproduct of cocaine (II) (1), is also a metabolic product of cocaine. The improved synthesis resulted from our efforts to understand cocaine photochemistry and our desire to synthesize labelled cocaine and its derivatives. The earlier reported synthesis of norcocaine, using potassium permanganate in a basic medium (2), gives 23% norcocaine together with *N*-benzoylecgonine methyl ester (III).



I II III IV

The improved synthesis of norcocaine was accomplished by controlling the *p*H of the reaction mixture. The potassium permanganate oxidation of cocaine is done in an acid medium to obtain 95% yield of norcocaine, based on recovered starting material. Cocaine (50%) and 5% *O*-benzoylecgonine (IV) were also isolated. Because *O*-acetyl and *O*-benzoyl groups of other related tropane derivatives are known to isomerize in basic media into the corresponding *N*-acetyl and *N*-benzoyl compounds and because the reverse reactions occur in acid media (3-5), the maintenance of a slightly acidic solution is important in the cocaine oxidation reaction in order to obtain high yields of norcocaine.

N-Benzoylecgonine methyl ester (III), obtained in basic oxidation conditions (2), was quantitatively converted into I in dry hydrogen chloride-dioxane. This is in accordance with the procedure of Fodor and Kovács (5) for the conversion of *N*-acetylnorpseudoecgonine ethyl ester into *O*-acetylnorpseudoecgonine ethyl ester hydrochloride.



III I

EXPERIMENTAL

Melting points and mixture melting points were obtained on a Fisher-Johns melting point apparatus and are corrected. The nuclear magnetic resonance spectra were taken on a Varian Associates A-60 instrument using tetramethylsilane as an internal standard and deuteriochloroform as solvent. The chemical shifts are given in δ values.

Thin layer chromatography was done on glass plates coated with neutral aluminum oxide 9F (Baker tlc Reagent). The plates were eluted with chloroform and visualized by ultraviolet light and iodine complexation.

Cocaine hydrochloride was supplied by Merck and Co., Inc. Free cocaine was obtained by neutralization of the hydrochloride with 10% ammonium hydroxide followed by extraction with ether and recrystallization of the solid obtained with ethanol, m.p. 98-99°, (lit. (6) m.p. 98°).

The procedure consisted of dissolving 2.53 g. of cocaine in 138 ml. of acetonitrile, 280 ml. of water, and sufficient acetic acid to make a slightly acidic solution. To this solution, 2.7 g. of potassium permanganate dissolved in 104 ml. of water was added dropwise over 10 hours with constant stirring and neutralization with dilute acetic acid. The solution was then stirred overnight and filtered. The volume of the filtrate was reduced under vacuum, bearing in mind that cocaine hydrolyzes in water (7). The reaction solution was then made slightly basic by solid potassium carbonate and extracted with ether.

The final isolation of norcocaine was achieved with column chromatography on neutral alumina using a benzene:chloroform mixture (60:40). Norcocaine (I), m.p. 78-80° (lit. (8) 80-82°), was identified by its nmr (deuteriochloroform): δ 8.2 (m, 2H of C_6H_5), 7.65 (m, 3H of C_6H_5), 5.5 (m, 1H, -C*H*OCOPh), 3.7 (s, 3H, $-CO_2CH_3$), 3.15 (s, 1H, -C*H*CO_2CH_3), and 1.75-2.50 (m, 8H, ring-CH_2 and CH). *O*-Benzoylecgonine, (IV), m.p. 196-197° (lit. (4) m.p. 199-201°) provided a related nmr (deuteriochloroform): δ 8.2 (m, 2H of C_6H_5), 7.6 (m, 3H of C_6H_5), 5.4 (m,

1H, -CHOCOPh), 3.15 (m, 1H, -CHCO$_2$H), 1.8-2.2 (m, 8H, ring CH$_2$ and CH protons), and 2.5 (s, 3H, N-CH$_3$).

The $N \rightarrow O$ migration was carried out by dissolving *N*-benzoylecgonine methyl ester (100 mg.) (III) in 2 ml. of dry, freshly distilled dioxane. To this solution 3 ml. of dry dioxane-hydrogen chloride (7.5 *N*) was added and refluxed for four hours on a water bath. Removal of solvent by reduced pressure and drying in vacuum left a hygroscopic, white solid. The amine was liberated by chloroform extraction of an aqueous sodium carbonate solution of the hydrochloride. Finally norcocaine (100 mg.) (I) was obtained by removal of chloroform.

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REFERENCES AND NOTES

(1) V. I. Stenberg, S. P. Singh, N. K. Narain and S. S. Parmar, unpublished results.

(2) G. Werner, R. Hackel, N. Mohammad, N. Seiler and K. H. Störr, *Ann. Chem.*, **708**, 210 (1967).

(3) A. Nickon and L. F. Fieser, *J. Am. Chem. Soc.*, 74, 5566 (1952).

(4) S. P. Findlay, *ibid.*, **76**, 2855 (1954).

(5) G. Fodor and O. Kovács, *J. Chem. Soc.*, 724 (1953).

(6) H. Steinmetz, *Ann. Chem.*, **434**, 133 (1923).

(7) A. Einhorn, *Ber.*, **21**, 47 (1888).

(8) H. L. Schmidt and G. Werner, *Ann. Chem.*, **653**, 184 (1962).