

Remarks on the Synthesis of Quaternary Cocaine Compounds

Sir:

We recently had the occasion to prepare several quaternary derivatives of cocaine for comparative pharmacological studies (1). Three such derivatives had previously been reported in the literature: methyl iodide (2), allyl bromide (3), and benzyl bromide (4). Of these references, only two describe any physical properties to support the assigned structures (2, 3), and we find a serious discrepancy with one of these (3). The difficulties encountered in the synthesis of these compounds prompted us to report our data concerning synthesis.

The methyl iodide quaternary of cocaine was prepared as described with little problem (2). Comparison of melting points plus supportive IR and NMR spectra and combustion analysis confirmed the structure.

Serious doubt, however, was raised on the reported isolation of the quaternary allyl bromide derivative of cocaine (3). Repetition of the procedure as described yielded a compound in good yield with the identical melting point as that reported, 186–187°. This proved to be the hydrobromide salt of cocaine as confirmed by IR and NMR spectra, combustion analysis, mixture melting point with an authentic sample, and conversion to and isolation of cocaine (free base) by treatment with saturated sodium bicarbonate solution. The latter test for all quaternary derivatives proved most valuable.

We have succeeded in preparing the quaternary allyl cocaine bromide by the reaction of cocaine with excess allyl bromide (1:10) in dimethylformamide in the presence of copper wire. Its melting point is 128–129°, and the structure was confirmed by IR and NMR spectra and combustion analysis. In addition, treatment with saturated sodium bicarbonate yielded no precipitate of cocaine.

However, several attempts to prepare the benzyl quaternary derivative of cocaine resulted only in the isolation of cocaine hydrobromide, m.p. 186–187°. Since the authors reporting this derivative, along with its pharmacology, cited no physical properties (4), the structure should be held in doubt until absolutely con-

firmed. We have suspected that we have obtained a mixture of the desired compound and the hydrobromide salt in our attempts, but have not as yet succeeded in isolating the quaternary in pure form.

A mixture also was presumably obtained in attempts to synthesize the ethyl quaternary iodide of cocaine. The NMR spectrum and combustion analysis of the reaction product, m.p. 140–144°, suggested that a small fraction of the mixture was the desired compound. The only product ultimately isolated, however, was the hydroiodide salt, m.p. 172–173°.

The other quaternary we prepared was the *n*-propyl iodide of cocaine. Treatment of cocaine with excess *n*-propyl iodide in a closed flask for several weeks gave a small yield of the desired compound, m.p. 155–156°. The structure was confirmed by combustion analysis and by its NMR spectrum.

Thus, caution in the interpretation of results in the preparation of alkyl quaternary halide derivatives of cocaine and of other sterically hindered bases is required. The predominant product using standard procedures is the simple hydrohalide salt of the tertiary base. Supportive evidence other than melting point and water solubility is mandatory.

Methods—All melting points were taken on a Fisher-Johns apparatus and are uncorrected. The IR spectra were recorded on either a Beckman IR-5 or IR-10 spectrophotometer in a KBr pellet. The NMR spectra were recorded on a Varian A-60 model in D₂O. Analyses were performed by Schwartzkopf Analytical Laboratories, Woodside, N. Y.

Methyl Cocaine Iodide—This compound was prepared from cocaine and methyl iodide (1:10), pale yellow platelets, m.p. 165–166°. [Lit. value, 169° (2).] Purification was accomplished from ethanol-ether. The IR spectrum exhibited carbonyl peaks at 1,705 and 1,730 cm.⁻¹. The NMR spectrum revealed a multiplet at 7.65 p.p.m. (5 H, aromatic), a quartet at 5.50 p.p.m. (1 H), a broad band at 4.20 p.p.m. (2 H, bridgehead), a singlet at 3.66 p.p.m. (3 H, OCH₃), a multiplet at 3.61 p.p.m. (1 H), 2 singlets at 3.10 and 3.20 p.p.m. [6 H, N⁺(CH₃)₂], and a broad multiplet at 2.33 p.p.m. (6 H, cycloaliphatic).

Anal.—Calcd. for C₁₈H₂₄INO₄: C, 48.54; H, 5.39; N, 3.15. Found: C, 48.23; H, 5.54; N, 2.99.

Allyl Cocaine Bromide—The reaction mixture, containing 3.0 g. (0.01 mole) of cocaine, 24.2 g. (0.20 mole) of allyl bromide, 10 ml. of dimethylformamide, and several pieces of copper wire, was sealed in a 50-ml. flask and stirred by a magnetic bar for a period of 3 days. The product was isolated by filtration and crystallized from ethanol-ether; white monoclinic prisms, m.p. 128–129°, in a yield of 3.2 g. (76%). Its IR spectrum exhibited carbonyl peaks at 1,705 and 1,727 cm^{-1} and lacked the presence of a strong shoulder from 3,000–2,500 cm^{-1} . The NMR spectrum was identical to that of the methyl quaternary with the exception of new multiplets at 5.74 p.p.m. (3 H, $\text{CH}=\text{CH}_2$) and a singlet at 2.83 p.p.m. (2 H, N^+CH_2-) in place of the singlet at 3.20 p.p.m. (3 H, N^+CH_3).

Anal.—Calcd. for $\text{C}_{20}\text{H}_{26}\text{BrNO}_4$: C, 56.60; H, 6.13; N, 3.30. Found: C, 56.27; H, 6.38; N, 3.40.

***n*-Propyl Cocaine Iodide**—A solution of cocaine and *n*-propyl iodide (1:10) was allowed to stand in a closed flask for 5 weeks. The reaction product was collected on a filter, washed with ether, and crystallized from ethanol-ether yielding fine white crystals, m.p. 155–156°, in a yield of 0.8 g. (17%). The IR spectrum was nearly identical to that of the methyl quaternary except in the fingerprint region. The NMR spectrum was identical to that of the methyl quaternary except for aliphatic absorption at 3.13 p.p.m. (2 H, N^+CH_2-), a multiplet at 1.21 p.p.m. (2 H), and a triplet at 0.59 (3 H, CH_3).

Anal.—Calcd. for $\text{C}_{20}\text{H}_{28}\text{INO}$: C, 50.77; H, 5.92; N, 2.96. Found: C, 50.87; H, 5.76; N, 2.95.

Cocaine Hydrobromide—The reaction as described (3) was conducted. A solution of 3.0 g. (0.01 mole) of cocaine and 6.0 g. (0.05 mole) of allyl bromide in 30 ml. of benzene was heated at reflux with stirring under a nitrogen atmosphere for a period of 5 hr.

The resulting precipitate was collected on a filter and crystallized from ethanol-ether. A yield of 3.1 g. (82%) of white crystals was obtained, m.p. 185–186°. (Lit. value, 186–187°). The IR spectrum exhibited a characteristic broad shoulder at 3,000–2,500 cm^{-1} (N^+H) plus the double carbonyl peaks at 1,732 and 1,705 cm^{-1} . Its NMR spectrum revealed the aromatic protons as a multiplet at 7.65 p.p.m. (5 H), a multiplet of 5.50 p.p.m. (1 H), a singlet at 4.58 p.p.m. (1 H, HOD), a broad band at 4.20 (2 H, bridgehead), a singlet at 3.66 (3 H, OCH_3), a multiplet at 3.56 p.p.m. (1 H), a triplet at 2.93 p.p.m. (3 H, N^+CH_3), and a multiplet at 2.33 p.p.m. (6 H, cycloaliphatic). Treatment of the product with saturated sodium bicarbonate solution led to the isolation of long, white needles of cocaine as the free base, m.p. 96°. A mixture melting point with an authentic sample of cocaine hydrobromide showed no depression, m.p. 185–186°.

Anal.—Calcd. for $\text{C}_{17}\text{H}_{22}\text{BrNO}_4$: C, 53.13; H, 5.73; N, 3.65. Found: C, 53.27; H, 5.86; N, 3.64.

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Books

REVIEWS

Microbial Transformation of Steroids and Alkaloids.

By HIROSHI ILZUKA and ATSHUSHI NAITO. University of Tokyo Press, Tokyo, Japan, 1967. U. S. Agent: University Park Press, State College, Pa. xi + 294 pp. 18.5 × 26 cm. Price \$16.50.

One approach to appraise the value of this book is to compare its contents to the two other books covering the same material ("Microbial Transformations of Steroids," by A. Capek *et al.*, Academic

Press, New York, 1965, and "Microbial Transformations of Steroids," a handbook, by W. Charney and H. L. Herzog, Academic Press, New York, 1967).

This monograph by Drs. Ilzuka and Naito is useful as a reference source for individuals who would like to find quickly the references to accomplish a certain microbial reaction on steroids and a few alkaloids. It is indexed according to the type of microbial reaction, name of microorganism, type of substances (substrates and products), and authors.