Synthesis of Morphine-d_5 and Codeine-d_8

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The synthesis of morphine labeled with deuterium in the *N*-methyl group and at positions 1 and 6 is described. Reduction of *N*-carboethoxy-1-bromonorcodeinone (IV) with lithium aluminum deuteride in tetrahydrofuran-d_8 yielded the codeine-d_5. *O*-Demethylation with sodium propylmercaptide-dimethyl formamide afforded morphine-d_5, which could be remethylated with perdeuterioiodomethane to give codeine-d_8. The labeled compounds are useful as standards for field ionization mass spectrometric analysis.

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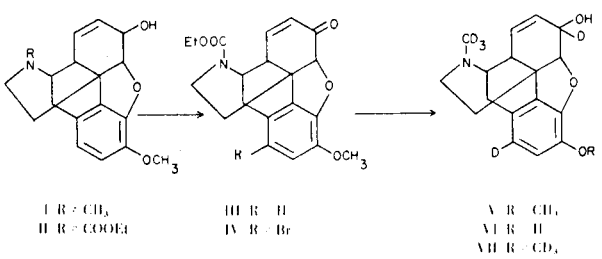
The application of field ionization mass spectrometry for the quantitative analysis of organic compounds has previously been reported (1). This type of mass spectrometry, which involves little or no fragmentation of the molecules, can be used to determine trace amounts of drugs in biological media by isotope dilution analysis with multilabeled dilutants. To apply this technique to the quantitative analysis of morphine and codeine, it was necessary to have available morphine-d_5 in order to overcome the background from the natural abundance of stable isotopes (1). The natural abundance of morphine M + 5 (molecular weight 290) is less than one part in 10^4 of the major isotopic species (molecular weight 285). The natural abundance of codeine M + 8 (molecular weight 307) is less than one part in 10^6. The synthesis of morphine labeled in the *N*-methyl group and at positions 1 and 6 is described. This multilabeled morphine was *O*-methylated with perdeuterioiodomethane to yield codeine-d_8. Both multilabled materials are being used as isotopic dilutants in the determination of these narcotic agents in urine.

Codeine (I) was readily demethylated (Scheme 1) on nitrogen *via* treatment with ethyl chloroformate (2) to afford *N*-carboethoxynorcodeine (II). The urethane was then oxidized to *N*-carboethoxynorcodeinone (III) by chromic acid-acetone (Jones reagent) in 97% yield. When the enone was allowed to react with an equivalent of bromine in acetic acid containing sodium acetate, bromination occurred predominantly at the 1-position to afford the key intermediate, *N*-carboethoxy-1-bromonorcodeinone (IV). In the absence of the sodium acetate, the hydrogen bromide produced during the bromination caused extensive decomposition of the enone.

Treatment of IV with lithium aluminum hydride in hot tetrahydrofuran caused reduction of the ketone and urethane groups to hydroxyl and *N*-methyl, respectively. However, the reflux time had to be extended to 72 hours in order to remove the bromine atom, yielding codeine (I) (3) in 70% yield. When **4** was similarly reduced with lithium aluminum deuteride, only 20% deuterium was incorporated at the 1-position following aqueous (water) workup as determined by proton nmr analysis. This suggested that an intermediate containing an aryl-metal bond was formed in the reduction and was subsequently decomposed to Ar-H by treatment with water. However, workup of the reaction with deuterium oxide still showed insufficient incorporation (75%) of deuterium on the aromatic ring. Since the tetrahydrofuran solvent was the only feasible proton source, the reaction was carried out in d_8-tetrahydrofuran with a deuterium oxide workup to afford codeine-d_5 (V) with 99% deuterium labels at C-1, C-6, and in the *N*-methyl group.

Scheme 1



I R = CH_3
II R = COOEt

III R = H
IV R = Br

V R = CH_3
VI R = H
VII R = CD_3

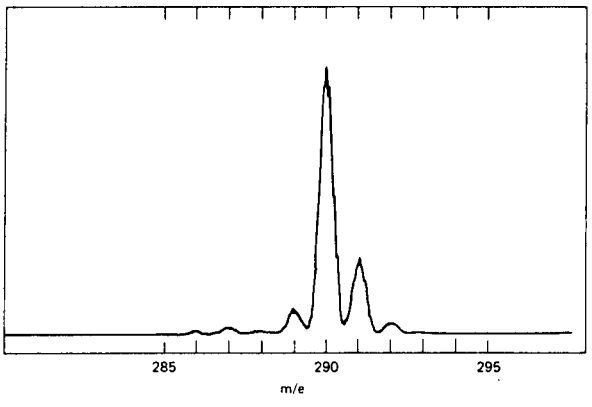


FIGURE 1 INTEGRATED MASS SPECTRUM OF d_5-MORPHINE (290)

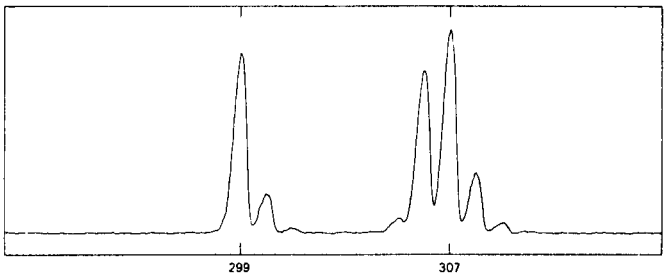


FIGURE 2 INTEGRATED MASS SPECTRUM OF CODEINE (299) AND d_8-CODEINE (307)

O-Demethylation of the codeine-d_5 was accomplished by treatment with sodium propylmercaptide in dimethyl formamide (4) at 110° to afford morphine-d_5 (VI) in 66% yield. A field ionization mass spectrum of morphine-d_5 is presented in Figure 1. *O*-Methylation of the morphine with perdeuterioiodomethane resulted in codeine-d_8 (VII). The field ionization mass spectrum of a mixture of codeine and codeine-d_8 is presented in Figure 2.

EXPERIMENTAL

N-Carboethoxynorcodeine (II).

To a mixture of 20.0 g. (66 mmoles) of codeine, 10.0 g. of potassium carbonate and 250 ml. of ethylene dichloride was added 20.0 ml. of ethyl chloroformate. This mixture was heated at reflux for 15 minutes, when another 10.0 g. of potassium carbonate and 20.0 ml. of ethyl chloroformate were added and reflux continued for one hour. Salts were removed by filtration and the filtrate evaporated *in vacuo*. The residue was dissolved in 100 ml. of methanol and treated with 25 ml. of 10% potassium hydroxide in methanol. The methanol was evaporated *in vacuo* and the residue partitioned between 200 ml. of dichloromethane and 80 ml. of 3*N* hydrochloric acid. The aqueous portion was extracted with another 50 ml. of dichloromethane and the combined organic solutions were dried over magnesium sulfate and evaporated *in vacuo* to leave 17.5 g. of a syrup; ir 3.0 (OH), 5.90 (N-COOEt); nmr (deuteriochloroform): 6.55 (2H, q, Ar-H, J = 8 Hz), 5.75 + 5.20 (2H, m, olefins, J_{AB} = 10 Hz), 4.85 (1H, d, C-5*H*, J = 7 Hz), 4.20 (2H, q, $COOCH_2CH_3$), 3.85 (3H, s, OCH_3), 1.25 (3H, t, $COOCH_2CH_3$).

N-Carboethoxynorcodeinone (III).

A solution of 4.3 g. (43 mmoles) of chromic acid in 4 ml. of concentrated sulfuric acid was diluted to a volume of 18 ml. with water. This solution was in turn added dropwise over 5 minutes to 14.1 g. (39.4 mmoles) of II in 300 ml. of acetone with maintenance of the temperature below 25°. The acetone layer was decanted and evaporated *in vacuo*. The residue was partitioned between 200 ml. of dichloromethane and 100 ml. of water. After drying, the organic phase was evaporated to leave a yellow oil which was chromatographed on 500 g. of silica gel with elution by chloroform-methanol (19:1) to afford 13.5 g. (95%) of product; tlc (silica gel, chloroform-methanol, 19:1), R_f 0.60; ir 5.9-6.0 μ (urethane + enone C=O; nmr (deuteriochloroform): 6.70 (2H, q, Ar-H, J = 8 Hz), 6.00 and 6.70 (2H, m, olefin, J = 10 Hz), 4.70 (1H, s, C-5), 4.20 (2H, q, $COOCH_2CH_3$), 3.85 (3H, s, OCH_3), 1.25 (3H, t, $COOCH_2CH_3$).

N-Carboethoxy-1-bromonorcodeinone (IV).

A solution of 8.0 g. (22.0 mmoles) of III in 80 ml. of acetic acid containing 6.4 g. (78 mmoles) of sodium acetate was treated dropwise with bromine (1.2 ml., 22.0 mmoles) until persistence of color. The solvent was removed *in vacuo* and the residue was partitioned between 100 ml. of dichloromethane and 100 ml. of water. The organic extract was washed with 50 ml. of saturated sodium bicarbonate, 50 ml. of water, dried over magnesium sulfate and evaporated to leave 9.5 g. (96%) of crude product. The material was chromatographed on a silica gel column with elution by ethyl acetate-dichloromethane (1:9) to afford 5.1 g. (53%) of a pale yellow gum; tlc, single spot, (silica gel, chloroform-methanol, 19:1); nmr (deuteriochloroform): 6.95 (1H, s, Ar-H), 6.75, 6.10 (2H, m, olefin, J_{AB} = 10 Hz), 4.95 (1H, s, C-5*H*), 4.15 (2H, q, $COOCH_2CH_3$), 3.90 (3H, s, OCH_3), 1.35 (3H, t, $COOCH_2CH_3$).

Codeine-*N*-C^2H_3-1,6-$^2H_2$ (V).

To a stirred solution of 5.80 g. (13.4 mmoles) of the bromoenone (IV) in 24 ml. of tetrahydrofuran-d_8 was slowly added 0.65 g. (15.4 mmoles) of powdered lithium aluminum deuteride. The mixture was slowly warmed to boiling and maintained at reflux for 72 hours. The solvent was removed by distillation and the residue was treated with 30 ml. of deuteriomethanol-deuterium oxide (9:1) by dropwise addition. The mixture was stirred for 10 minutes, diluted with 100 ml. of ether and dried over magnesium sulfate. The solvent was removed *in vacuo* to leave 3.00 g. (60%) of a syrup which crystallized on standing; tlc (silica gel, chloroform-methanol-trimethylamine, 90:9:1), R_f 0.40, identical to authentic codeine; nmr (deuteriochloroform): 6.65 (1H, s, ArH), 5.70, 5.20 (2H, m, olefin, J_{AB} = 10 Hz), 4.90 (1H, s, C-5H), 3.85 (3H, s, OCH_3); fims m/e 304.

In an unlabeled run, the product was found to be identical with codeine in all respects.

Morphine-*N*-C^2H_3-1,6-$^2H_2$ (VI).

An ice cold solution of 1.00 g. (3.3 mmoles) of codeine-d_5 (V) in 40 ml. of dry dimethyl formamide was degassed under nitrogen. Potassium *t*-butoxide (1.00 g., 8.9 mmoles) was added followed by further degassing to remove oxygen and injection of 1.00 ml. (10.9 mmoles) of propanethial. The mixture was heated at 110° under nitrogen for 3.5 hours, cooled, and acidified with 1.0 ml. of acetic acid. The solvent was removed *in vacuo* to leave an orange residue which was partitioned between 40 ml. of ether and 45 ml. of 0.5 *N* hydrochloric acid. The aqueous portion was twice washed with 40 ml. portions of ether and treated with 5 ml. of 20% sodium bisulfite. The aqueous extract was treated with Norite and adjusted

to *p*H 9 with concentrated ammonium hydroxide. The off-white precipitate was collected to afford 0.63 g. (66%) of morphine-d_5, m.p. 238-240° (authentic morphine, m.p. 246-248°); tlc (silica gel, chloroform-methanol-trimethylamine, 90:1:1), R_f 0.20, identical with morphine; fims, m/e 290.

Remethylation of the morphine-d_5 with deuteromethyl iodide (sodium hydride-DMF at -25°) afforded codeine-d_8 (VII) in 12% yield; fims, m/e 307.

Acknowledgment.

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