8β-Substituted Dihydrocodeinones Having Heteroatoms in the Side Chain (1)

Michael P. Kotick and Joseph O. Polazzi*

Chemistry Department, Corporate Research Division, Miles Laboratories, Incorporated, Elkhart, Indiana 46515

Received January 19, 1981

A series of 8β-substituted dihydrocodeinones, having hetero atoms in the side chain, were prepared. Michael addition of methanol or ethanol to **1** was accomplished under basic conditions, while the nitromethane adduct was prepared by a fluoride ion catalyzed reaction. The 8β-diethylmalonyl adduct **7** was converted in several steps to an 8β-tertiary carbinol analog **12**. Alternatively, 8β-vinyldihydrocodeinone **13** was transformed, *via* the dimethyl ketal, to 8β-hydroxymethyl or -ethyl compounds which were fluorinated in the side chain by use of diethylaminosulfur trifluoride.

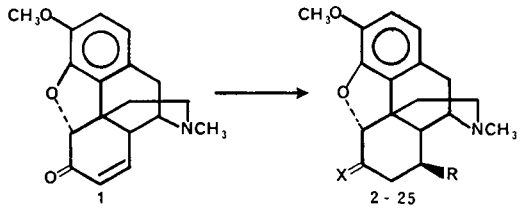
J. Heterocyclic Chem., **18**, 1029 (1981).

We have recently reported modification in the analgesic and narcotic antagonist properties of 17-cycloalkylmethylmorphinan compounds by the introduction of short alkyl groups into the 7- (2) and 8- (3) positions of this polycyclic system. To extend these observations further, particularly with regard to 4,5α-epoxymorphinan-6-one compounds, we now report other modifications of the 8β-position. These new analogs, containing hetero atoms in the side chain, were prepared by the formation of carbon-carbon or carbon-hetero bonds by Michael-type addition reactions or by transformation of our previously reported (3a) 8β-vinyldihydrocodeinone (**13**). The preparation of 8β-hydroxyethylthiodihydrocodeinone (**2**) by conjugate addition of mercaptoethanol to codeinone (**1**) has been reported by us in connection with the purification of 7β,8β-methanodihydrocodeinone (1). Easy cleavage of the cyclopropane ring in this latter compound with dilute hydrochloric acid yielded 8β-chloromethyldihydrocodeinone (**3**).

A survey of the literature revealed that several other 8-substituted dihydrocodeinones have been prepared. The piperidine, morpholine, nitromethane and diethyldithiocarbamic acid adducts of **1** were reported some time ago (4). 14-Hydroxycodeinone undergoes addition of ethylene glycol to the 8-position, concurrent with ketalization, under acidic conditions (5). The facile hydration of 14-hydroxymorphinone with aqueous base to give an 8,14-dihydroxy derivate has also been reported (6). Attempted ketalization of **1** with trimethyl orthoformate, methanol and acid gives the methyl enol ether of 8-methoxy-dihydrocodeinone (7), which was hydrolyzed by acid to **4**. Most recently, the preparation of 8β-halogeno-dihydrocodeinones by the addition of hydrogen chloride or bromide to neopinone, as intermediates for a preparation of **1**, were described (8).

We found that **1** reacted readily with methanol or ethanol in the presence of aqueous base. Although thin layer chromatography indicated good conversion to **4** or **5**, these compounds proved to be unstable and were isolated

Table I



Compound No.	X	R	ED_{50} (μmole/Kg) (a)
1			IA (b) 3.0 (c)
2	O	SCH_2CH_2OH	IA 25.
3	O	CH_2Cl	12.3 (8.9-17.)
4	O	OCH_3	26.7 (9.4-82.)
5	O	OCH_2CH_3	IA 30
6	O	CH_2NO_2	IA 30
7	O	$CH(COOCH_2CH_3)_2$	IA 30
8	O	$CH_2COOCH_2CH_3$	IA 30
9	O	CH_2COOH	IA 30
10	$(CH_3CH_2O)_2$	$CH_2COOCH_2CH_3$	——
11	$(CH_3CH_2O)_2$	$CH_2COH(CH_3)_2$	——
12	O	$CH_2COH(CH_3)_2$	IA 30
13	O	$CH=CH_2$	13.8 (3.9-50.)
14	$(CH_3O)_2$	$CH=CH_2$	——
15	$(CH_3O)_2$	CH_2CH_2OH	——
16	O	CH_2CH_2OH	16.6 (9.3-29.)
17	$(CH_3O)_2$	CH_2CHO	——
18	$(CH_3O)_2$	CHO	——
19	$(CH_3O)_2$	CH_2OH	——
20	O	CH_2OH	IA 10
21	O	CH_2CH_2F	6.4 (2.9-13.)
22	$(CH_3O)_2$	CH_2CHF_2	——
23	O	CH_2CHF_2	10.0 (1.3-83.)
24	O	CH_2F	17.5 (12.4-25.)
25	O	SCH_2CH_2F	19.4 (9.9-39.)
Dihydrocodeinone	O	H	2.4 (1.6-3.6)
Dihydrocodeine	HO---, H	H	3.8

(a) Antinociceptive ED_{50} in mouse writhing assay, μmoles/Kg (95% confidence limits). Salts were administered in distilled water; free bases were dissolved by addition of dilute hydrochloric acid and further diluted. Ketals were not tested. (b) IA = Inactive at dose indicated. (c) Causes convulsions at higher doses.

0022-152X/81/051029-05$02.25

in low final yields after purification. The previously reported adduct **6** (4), was prepared in enhanced yield by naked fluoride ion catalyzed (9) reaction with nitromethane in refluxing acetonitrile. Confirmation of the expected β configuration of the C-8 appendage, both in these cases and those reported below, is based on the singlet nuclear magnetic resonance signal observed for the aromatic protons in agreement with our previous observations (3a) on isomeric 8-alkyldihydrocodeinones.

Compound **1** quickly added sodio diethylmalonate at room temperature to give a nearly quantitative yield of adduct **7**. This was decarboxylated and esterified to give a moderate yield of **8**. The free acid **9** was obtained by saponification. Conversion of **8** to the diethyl ketal **10** followed by reaction with methyl lithium gave tertiary carbinol side chain derivative **11** which was hydrolyzed to the 6-oxo compound **12** with ethanolic hydrochloric acid. Compounds of type **12** were of interest as analogs of the potent analgesic *endo*ethenotetrahydrothebaines (10).

The side chain functionality of the 8β-vinyl compound **13** allowed preparation of derivatives containing hydroxy or fluoride groups. The dimethyl ketal **14**, upon treatment with 9-borabicyclo[3.3.1]nonane (11) in toluene at 80°, gave a good yield of protected 8β-hydroxyethyl compound **15** which was hydrolyzed to the free ketone **16**. Alternatively, oxidation of **15** by use of dimethylsulfoxide-trifluoroacetic anhydride (12) at -60° gave the aldehyde **17**. Cleavage of the terminal methylene group of **14**, to give aldehyde **18**, was effected by the Lemieux-Johnson oxidation procedure (catalytic osmium tetroxide-periodate) (13). Reduction of the intermediate ketal **18** with lithium aluminum hydride followed by hydrolysis gave the 8β-carbinol **20**.

Conversion of the side chain alcohols to monofluoro derivatives **21** and **24** was conveniently done using diethylaminosulfur trifluoride (DAST) (14). Reaction of the 6-oxo-8β-hydroxyalkyl compounds with two equivalents of DAST in methylene chloride solution was carried out for a short time at 0° to minimize reaction at the ketone function. The major side product, responsible for the low overall yield in these reactions, contained a diethylamino group (15) as indicated by nmr and was not further characterized. The 8β-fluoroethylthio compound **25** was prepared from **2** in a similar manner. The protected aldehyde **17** was converted to the difluoro compound **22** by reaction with DAST in toluene solution at 50°. Acid hydrolysis gave the desired 6-oxo-difluoro derivative **23** in moderate yield.

The 6-oxo compounds included in this report were tested for antinociceptive activity in the mouse writhing assay (16) using acetic acid as the noxious stimulus. None of the compounds showed exceptional activity when compared with dihydrocodeine or dihydrocodeinone. These pharmacological results, in line with our previous observations (2,3), indicate that an area of bulk intolerance exists in the 8β region of the opiate receptor. Our efforts directed toward determining the factors responsible for the high potency of the *endo*ethanotetrahydrothebaines continue.

EXPERIMENTAL

Methods have previously been described (3a). Processing in the usual fashion implies that the organic extracts were combined, washed with dilute ammonia solution, dried over anhydrous magnesium sulfate and evaporated to dryness under water aspirator vacuum on a rotary evaporator. These residues were finally dried at 50-60° bath temperature using a mechanical vacuum pump. Column chromatography was carried out over Silica Gel G (E. Merck), usually with a loading factor of ~1.0 g of the mixture to 100 g of gel and chloroform-methanol mixtures (4:1 to 15:1) containing 1.0 to 0.5% v/v concentrated ammonium hydroxide as eluant. Nuclear magnetic resonance spectra (nmr) were determined in deuteriochloroform. Mass spectra (ms) were determined by using a Hewlett-Packard 5985A GC/MS system and are reported as m/e (relative intensity). Ir spectra were determined in deuteriochloroform.

8β-Methoxydihydrocodeinone (**4**).

To a solution of **1** (1.50 g, 5 mmoles) in methylene chloride (15 ml) and methanol (75 ml), cooled in an ice bath, was added 5*N* sodium hydroxide (1 ml.). Stirring was continued in the cold for 2 hours, the mixture evaporated to dryness and the residue partitioned between water and chloroform. Processing in the usual fashion gave 1.50 g of a foam which was chromatographed to give 975 mg (59%) of **4** as crystals after removal of the solvent. Recrystallization from ethanol gave 586 mg of **4**, mp 194-196° [lit. (7) mp 195-197°]; nmr: δ 2.47 (-NCH_3), 3.27 (s, 8β-OCH_3), 3.93 (3-OCH_3), 4.68 (s, H5), 6.83 (s, aromatic).

Anal. Calcd. for $C_{19}H_{23}NO_4$: C, 69.28; H, 7.04; N, 4.25. Found: C, 69.51; H, 7.23; N, 4.21.

8β-Ethoxydihydrocodeinone (**5**).

Compound **1** (2.0 g, 6.7 mmoles) in methylene chloride (30 ml) and ethanol (50 ml) was cooled in an ice bath and 5*N* sodium hydroxide solution (1.4 ml) added. After stirring for 1 hour, an additional 1.4 ml of sodium hydroxide solution was added and stirring continued for an additional 45 minutes. Workup as above followed by chromatography gave 557 mg (24%) of **5** as a foam. Crystallization from ethanol gave pure **5**, mp 145-147°; nmr: δ 1.14 (t, -CH_2-CH_3), 2.47 (-NCH_3), 3.93 (3 -OCH_3), 4.70 (s, H5), 6.72 (s, aromatic).

Anal. Calcd. for $C_{20}H_{25}NO_4$: C, 69.95; H, 7.34; N, 4.08. Found: C, 70.04; H, 7.40; N, 4.04.

8β-Nitromethyldihydrocodeinone (**6**).

A mixture of **1** (11.88 g, 40 mmoles), potassium fluoride (0.48 g, 8.3 mmoles), 18-crown-6-ether (0.24 g, 0.9 mmole), and nitromethane (50 ml) in acetonitrile (350 ml) was refluxed for 7 hours. The mixture was evaporated and the residue partitioned between dilute ammonia and chloroform. Further processing followed by evaporation gave a syrup which crystallized from ethanol to give 8.38 g (59%) of **6** as brown crystals, mp 182-185°. Recrystallization from ethanol gave 6.14 g of pure **6**, mp 198-201° [lit. (4) mp 197-200°]; nmr: δ 2.45 (-NCH_3), 3.90 (-OCH_3), 4.44 (unsymmetrical d, 2H, -CH_2NO_2, J = 5 Hz), 4.66 (s, H5), 6.80 (s, aromatic).

Anal. Calcd. for $C_{19}H_{22}N_2O_5$: C, 63.68; H, 6.19; N, 7.82. Found: C, 63.41; H, 6.31; N, 7.64.

8β-Diethylmalonyldihydrocodeinone (**7**).

Sodium hydride (57% in mineral oil, 1.40 g, 33 mmoles) under an argon atmosphere was washed several times with hexane and then suspended in toluene (75 ml). To this was added diethyl malonate (5.28 g, 33 mmoles) and the mixture stirred for 30 minutes at room temperature.

To this suspension was added rapidly dropwise a warm solution of **1** (8.91 g, 30 mmoles) in toluene (150 ml) and the mixture stirred at ambient temperature for 30 minutes. The mixture was poured into saturated ammonium chloride solution (300 ml) and stirred for 15 minutes. The organic phase was separated and further processed in the usual fashion to give **7** (15.5 g) as a syrup. Crystallization of a portion of this material from ethanol-ether, then ethanol, gave crystals of **7**, mp 128-129°; nmr: δ 1.07-1.50 (m, -CH_3), 2.43 (-NCH_3), 3.56 (d, 1H, -CH-, J = 4 Hz), 3.97-4.43 (q, 4H, -CH_2-), 4.65 (s, H5), 6.67 (s, aromatic).

Anal. Calcd. for $C_{25}H_{31}NO_7$: C, 65.63; H, 6.83; N, 3.06. Found: C, 65.51; H, 7.02; N, 3.11.

8β-Ethoxycarbonylmethyldihydrocodeinone (**8**).

A warm solution of **7** (3.89 g, 8.5 mmoles) in ethanol (50 ml) was cooled and diluted with water (30 ml). Potassium hydroxide solution (1*N*, 30 ml) was added and the mixture kept at room temperature for 2 hours and then evaporated to dryness. The residue was dried by azeotropic evaporation, first with ethanol-toluene and then toluene. The dry residue was suspended in ethanol (100 ml) and concentrated hydrochloric acid (4.5 ml) added. The mixture was refluxed for 18 hours and then evaporated to dryness. The residue was dissolved in water, excess concentrated ammonia added and the mixture extracted with three protions of chloroform. Processing in the usual fashion gave 3.16 g of a foam which was chromatographed to give 2.72 g (83%) of **8** as a crystalline solid. Recrystallization from ethyl acetate gave an analytical sample of **8**, mp 128-130°; nmr: δ 1.22 (t, 3H, -CH_2CH_3), 2.44 (-NCH_3), 3.93 (-OCH_3), 4.10 (q, 2H, -$COOCH_2$-), 4.65 (s, H5), 6.88 (s, aromatic).

Anal. Calcd. for $C_{22}H_{27}NO_5$: C, 68.55; H, 7.06; N, 3.63. Found: C, 68.52; H, 7.06; N, 3.66.

8β-Carboxymethyldihydrocodeinone (**9**).

A suspension of **8** (771 mg, 2 mmoles) in ethanol (20 ml) and water (20 ml) was warmed until solution occurred and 1*N* sodium hydroxide (3 ml) added. The mixture was stirred at room temperature for 30 minutes, 1*N* hydrochloric acid (3 ml) added and the mixture evaporated to a thick syrup. Crystals which formed on the addition of acetone were collected and recrystallized from aqueous acetone to give 331 mg (47%) of **9**, mp > 270°; nmr: δ 2.67 (-NCH_3), 3.93 (3-OCH_3), 4.92 (s, H5), 6.80 (s, aromatic), 8.27 (s, 1H, -COO*H*).

Anal. Calcd. for $C_{20}H_{23}NO_5$: C, 67.31; H, 6.49; N, 3.92. Found: C, 67.61; H, 6.55; N, 3.96.

8β-Ethoxycarbonylmethyldihydrocodeinone Diethyl Ketal (**10**).

A mixture of **9** (1.0 g, 2.6 mmoles), triethyl orthoformate (1.7 g, 11.7 mmoles) and concentrated sulfuric acid (0.16 ml) in ethanol was refluxed overnight. The solution was evaporated, diluted with aqueous ammonia and extracted with chloroform. Processing in the usual fashion gave 1.2 g of a syrup which was shown to consist of a mixture of the ketal **10** and the ethyl enol ether of **9** by nmr. Compound **10** had nmr: δ 0.73-1.0 (1t, 3H, -CH_2CH_3), 1.0-1.3 (2t, 6H, -OCH_2CH_3), 2.42 (-NCH_3), 3.93 (3-OCH_3), 4.48 (s, H5), 6.63 (m, aromatic).

8β-(2-Hydroxy-2-methyl)propyldihydrocodeinone (**12**).

A solution of the diethyl ketal **10** (2.00 g, 4.35 mmoles) in ether (50 ml) was cooled in an ice bath and methyl lithium (17.4 mmoles, 1.6 molar in ether) added dropwise. The mixture was stirred for 1 hour at 0° and quenched by pouring into saturated ammonium chloride solution. The organic layer was separated and the aqueous phase washed with several portions of chloroform. The organic phases were processed in the usual fashion and evaporated to give **11**, obtained as a foam. This compound has nmr: δ 0.80-1.06 (t, -CH_2CH_3), 1.17 (s, 6H, $C(CH_3)_2$), 2.40 (-NCH_3), 3.90 (3-OCH_3), 4.45 (s, H5), 6.58 (m, aromatic).

The foam was boiled with ethanol (20 ml) and 1*N* hydrochloric acid (10 ml) on the steam bath for 15 minutes. The mixture was cooled, concentrated and dissolved in water. After the addition of excess concentrated ammonia, extraction with chloroform and processing in the usual fashion gave 1.3 g of a syrup which was chromatographed. The desired product **12**, 718 mg (48%), was obtained in crystalline form on pooling and evaporation of homogeneous fractions. Recrystallization from methanol-ether gave pure **12**, mp 185-187°; nmr: δ 1.15 (s, 6H, -$C(CH_3)_2$), 2.42 (-NCH_3), 3.90 (3-OCH_3), 4.65 (s, H5), 6.63 (s, aromatic).

Anal. Calcd. for $C_{22}H_{29}NO_4$: C, 71.13; H, 7.87; N, 3.77. Found: C, 71.02; H, 7.83; N, 3.81.

8β-Vinyldihydrocodeinone Dimethyl Ketal (**14**).

To a mixture of **13** (3a) (13.0 g, 40 mmoles) and trimethyl orthoformate (13.3 g, 125 mmoles) in methanol (160 ml) was added dropwise, concentrated sulfuric acid (3.7 ml, 67 mmoles). The mixture was refluxed for 3 hours, cooled and concentrated ammonium hydroxide (25 ml) was added. The mixture was concentrated to remove the bulk of the methanol, diluted with aqueous ammonia and extracted with chloroform. Processing in the usual fashion gave 19.8 g of a syrup which contained traces of impurities in addition to **14**. Material prepared in another reaction was chromatographed to give a 68% yield of **14** which was obtained as a syrup, homogeneous by tlc; nmr: δ 2.41 (-NCH_3), 3.13 (s, 6α-OCH_3), 3.37 (s, 6β-OCH_3), 4.55 (s, H5), 4.88 (d of doublets, J = 2 and 7 Hz, =CH_2), 5.10 (s, 1H, =CH_2), 5.47-6.13 (complex m, 1H, -CH=), 6.70 (d, 2H, J = 3 Hz, aromatic); ms: m/e 371 (53), 356 (29), 324 (41), 267 (30), 266 (32), 127 (100), 59 (30).

Anal. Calcd. for $C_{22}H_{29}NO_4$: C, 71.13; H, 7.87; N, 3.77. Found: C, 70.79; H, 8.21; N, 3.53.

8β-Hydroxyethyldihydrocodeinone Dimethyl Ketal (**15**).

To a solution of the dimethyl ketal **14** (prepared from 40 mmoles of **1**) in toluene (400 ml) under argon was added 9-borabicyclo[3.3.1]nonane (0.5*M* in tetrahydrofuran, 112 ml, 56 mmoles). The mixture was heated to 80° and kept at this temperature for 2 hours. The mixture was cooled and the following added sequentially dropwise: ethanol (40 ml), 1*N* sodium hydroxide (80 ml) and 30% hydrogen peroxide (30 ml). The mixture was heated at 50° for 45 minutes, cooled and the organic phase separated. After washing with dilute ammonia, the organic phase was evaporated to dryness to give 11.95 g (77%) of **15** as a white solid, homogeneous by tlc. Recrystallization of a portion of this material from methanol gave an analytical sample of **15**, mp 170-172°; nmr: δ 2.40 (-NCH_3), 3.08 and 3.33 (s, 6-OCH_3's), 3.62 (m, 2H, -CH_2CH_2OH), 3.88 (3-OCH_3), 4.48 (s, H5), 6.63 (m, aromatic).

Anal. Calcd. for $C_{22}H_{31}NO_5$: C, 67.84; H, 8.02; N, 3.60. Found: C, 67.67; H, 7.96; N, 3.61.

8β-Hydroxyethyldihydrocodeinone (**16**).

A solution of the ketal **15** (5.35 g, 13.7 mmoles) in ethanol (50 ml) and 1*N* hydrochloric acid (30 ml) was heated on the steam bath for 20 minutes. The mixture was evaporated to a small volume, made basic by the addition of ammonia and extracted with methylene chloride. The organic phases were processed in the usual fashion. Evaporation gave a crystalline residue (4.03 g, 85%) which was twice crystallized from ethanol to give pure **16**, mp 218-220°; nmr: δ 2.47 (-NCH_3), 3.32-3.75 (m, -CH_2CH_2OH), 3.92 (3-OCH_3), 4.73 (s, H5), 6.68 (m, aromatic).

Anal. Calcd. for $C_{20}H_{25}NO_4$: C, 69.95; H, 7.34; N, 4.08. Found: C, 69.74; H, 7.59; N, 4.06.

8β-Ethanaldihydrocodeinone Dimethyl Ketal (**17**).

A solution of trifluoroacetic anhydride (2.2 ml, 15.6 mmoles) in methylene chloride (5 ml) was added slowly dropwise to a -60° solution of dimethyl sulfoxide (1.5 ml, 21.2 mmoles) in methylene chloride (15 ml) under an argon atmosphere. After stirring for 10 minutes, a solution of **15** (3.90 g, 10 mmoles) in methylene chloride (20 ml) was added dropwise while maintaining the -60° temperature. The mixture was stirred for 1 hour at -60°, then triethylamine (4 ml) added dropwise and the mixture allowed to warm to room temperature. The mixture was diluted with methylene chloride and washed 5 times with dilute ammonia. Drying and evaporation of the solvent gave 4.36 g of a foam which was shown by nmr to be a 3:1 mixture of **17** and **15**. Chromatography gave 1.95 g (50%) of pure **17** as a foam which could not be obtained in crystalline form; nmr:

2.43 (-NCH_3), 3.17 and 3.66 (6-OCH_3's), 3.93 (3-OCH_3), 4.52 (s, H5), 6.70 (m, aromatic); ms: m/e 387 (22); ir: 1720 cm^{-1} (-CHO).

8β-Formyldihydrocodeinone Dimethyl Ketal (**18**).

To a solution of **14** (1.90 g, 5.1 mmoles) in tetrahydrofuran (50 ml) and water (25 ml) was added several large crystals of osmium tetroxide. After stirring for several minutes, a solution of sodium metaperiodate (6.5 g, 30 mmoles) in water (60 ml) was added dropwise over a period of 90 minutes. Stirring was continued for an additional 30 minutes, then the mixture was filtered to remove insoluble material. The insolubles were washed with tetrahydrofuran and the filtrate evaporated to a small volume. Processing in the usual fashion gave a syrup which was chromatographed to give 668 mg (35%) of **18** at a syrup, homogeneous by tlc; nmr: δ 2.77 (-NCH_3), 3.13 and 3.30 (6-OCH_3's), 3.87 (3-OCH_3), 4.70 (d, H5, J = 1.5 Hz), 6.67 (d, aromatic, J = 2 Hz), 9.71 (s, -CHO); ms: m/e 373 (100); ir: 1725 cm^{-1} (-CHO).

8β-Hydroxymethyldihydrocodeinone Dimethyl Ketal (**19**).

A solution of **18** (600 mg) in ether (20 ml) was added dropwise to a suspension of lithium aluminum hydride (100 mg) in ether (10 ml). The mixture was stirred for 30 minutes and the excess of hydride destroyed by the addition of water. After filtration through Celite, the filtrate was washed with dilute ammonia and evaporated to give **19** as a foam; nmr: δ 2.40 (-NCH_3), 3.13 and 3.30 (6-OCH_3's), 3.60 (m, -CH_2OH), 3.90 (3-OCH_3), 4.47 (s, H5), 6.63 (m, aromatic); ms: m/e 375 (100), 360 (60), 344 (70), 343 (51), 342 (48), 328 (84), 312 (58), 272 (31), 271 (56), 270 (66), 206 (63), 131 (68), 71 (26), 42 (31); ir: 3625 cm^{-1} (-OH).

8β-Hydroxymethyldihydrocodeinone (**20**).

The above foam was dissolved in a mixture of 1*N* hydrochloric acid (5 ml) and ethanol (5 ml) and boiled on the steam bath for 20 minutes. The mixture was diluted with ice, made basic by the addition of concentrated ammonium hydroxide and extracted with chloroform. Processing in the usual manner gave **20** as a foam which gave crystals, mp 199-200°, on the addition of ethyl acetate; nmr: δ 2.45 (-NCH_3), 3.60 (m, -CH_2OH), 3.93 (3-OCH_3), 4.67 (s, H5), 6.68 (s, aromatic).

Anal. Calcd. for $C_{19}H_{23}NO_4$: C, 69.28; H, 7.04; N, 4.25. Found: C, 69.74; H, 7.24; N, 3.93.

8β-(2-Fluoroethyl)dihydrocodeinone (**21**).

A solution of **16** (2.78 g, 8.1 mmoles) in methylene chloride (100 ml) under argon was added over 30 minutes to a solution of diethylaminosulfur trifluoride (4.5 g, 24 mmoles) in methylene chloride (75 ml) at 0°. The reaction was kept at 0° for 30 minutes and quenched by the addition ofa mixture of concentrated ammonia (20 ml) and water (50 ml). Further processing in the usual manner gave 3.2 g of a yellow gum which was chromatographed to give 788 mg (28%) of **21** which crystallized and was recrystallized from ethanol-ether to give pure **21**, mp 145-146°; nmr: δ 2.47 (-NCH_3), 3.95 (3-OCH_3), 4.02 and 4.83 (m, 2H, J = 47 and 7 Hz, -CH_2F), 4.72 (s, H5), 6.73 (m, aromatic).

Anal. Calcd. for $C_{20}H_{24}FNO_3$: C, 69.54; H, 7.00; N, 4.06. Found: C, 69.54; H, 7.04; N, 3.99.

8β-(2,2-Difluoroethyl)dihydrocodeinone Dimethyl Ketal (**22**).

To a solution of **17** (1.87 g, 4.8 mmoles) in toluene (60 ml) under argon at 50° was added diethylaminosulfur trifluoride (2.58 g, 16 mmoles) in toluene (10 ml) and the mixture kept at 50° for 3 hours. The reaction was cooled in ice and quenched by the dropwise addition of concentrated ammonia (10 ml) in water (20 ml). The toluene layer was separated, evaporated and the residue taken up in methylene chloride. The aqueous phase was washed with two portions of methylene chloride, the combined organic phases washed with water, dried and evaporated to give a mixture of **15** and the faster migrating (tlc) **22**. Chromatography gave **22** (600 mg, 30%) as a yellow oil which crystallized on standing in ethanol. Recrystallization from ethanol gave pure **22**, mp 140-142°; nmr: δ 2.42 (-NCH_3), 3.15 and 3.35 (6-OCH_3's), 3.95 (3-OCH_3), 4.50 (H5), 4.67-5.90 (complex, 1H, -C*H*F_2), 6.67 (m, aromatic); ms: m/e 409 (100), 394 (416), 362 (37), 304 (32), 165 (88).

Anal. Calcd. for $C_{22}H_{29}F_2NO_4$: C,64.53; H, 7.14; N, 3.42. Found: C, 64.85; H, 7.49; N, 3.29.

8β-(2,2-Difluoroethyl)dihydrocodeinone (**23**).

The above ketal (**22**, 600 mg) was gently heated on the steam bath with 1*N* hydrochloric acid (5 ml) and ethanol (10 ml) for 15 minutes. The mixture was concentrated to remove the ethanol, dilute ammonia added and the mixture extracted with chloroform. Evaporation of the organic extracts gave 463 mg of a dark syrup which was chromatographed to give 386 mg (72%) of pure **22** as a foam. The hydrochloride salt, mp > 250°, crystallized from methanol-ethyl acetate. The free base had nmr: δ 2.47 (-NCH_3), 3.93 (3-OCH_3), 4.68 (H5), 4.76-5.96 (complex, 1H, -C*H*F_2), 6.70 (s, aromatic).

Anal. Calcd. for $C_{20}H_{23}F_2NO_3$·HCl: C, 60.07; H, 6.05; N, 3.50. Found: C, 59.75; H, 6.04; N, 3.52.

8β-(Fluoromethyl)dihydrocodeinone (**24**).

A solution of **20** (1.50 g, 4.6 mmoles) in methylene chloride (30 ml) was slowly added under an argon atmosphere to diethylaminosulfur trifluoride (1.3 ml ~ 10 mmoles) in methylene chloride (10 ml) cooled in an ice bath. After 15 minutes, the reaction was quenched by the addition of a mixture of concentrated ammonia (10 ml) and water (25 ml). The organic phase was separated and processed in the usual manner to give 1.41 g of a yellow foam. The foam was chromatographed to give 470 mg (31%) of **24** as an oil which formed crystals, mp 166.5-167.5°, on standing in ethanol; nmr: 2.47 (-NCH_3), 3.97 (3-OCH_3), 4.72 (s, H5), 4.07 and 4.87 (d of doublets, 2H, J = 48 and 4 Hz, -CH_2F), 6.73 (s, aromatic).

Anal. Calcd. for $C_{19}H_{22}FNO_3$: C, 68.86; H, 6.69; N, 4.22. Found: C, 68.44; H, 6.79; N, 4.15.

8β-(2-Fluoroethylthio)dihydrocodeinone (**25**).

To a solution of diethylaminosulfur trifluoride (4.5 g, 28 mmoles) in methylene chloride (75 ml) cooled to 0° was added slowly dropwise a solution of the free base of **2** (3.59 g, 10 mmoles) in methylene chloride (75 ml). After the completion of the addition, the mixture was stirred for 15 minutes in the cold and quenched by the addition of concentrated ammonium hydroxide (20 ml) and water (50 ml). The organic layer was separated, dried, and evaporated to give a yellow foam which was chromatographed. Combination of fractions containing the faster migrating component gave 1.34 g (35%) of **25** as a syrup. The syrup was converted to the hydrochloride salt which gave crystals, mp 225-226°, from ethanol; nmr of free base: δ 2.45 (-NCH_3), 3.90 (3-OCH_3), 4.67 (s, H5), 4.07 and 4.87 (2t, J = 46 and 6 Hz, -CH_2F), 6.67 (s, aromatic).

Anal. Calcd. for $C_{20}H_{24}FNO_3S$·HCl: C, 58.03; H, 6.09; N, 3.38. Found: C, 58.30; H, 6.18; N, 3.43.

Acknowledgement.

We wish to thank Dr. J. F. Howes, SISA Incorporated, Cambridge, Massachusettes, for the pharmacological results.

REFERENCES AND NOTES

(1) Analgesic Narcotic Antagonists. 7. For Part 6, see M. P. Kotick, *J. Med. Chem.*, **24**, 722 (1981).

(2a) D. L. Leland and M. P. Kotick, *ibid.*, **23**, 1427 (1980); (b) D. L. Leland and M. P. Kotick, *ibid.*, **24**, 717 (1981), Part 5.

(3a) M. P. Kotick, D. L. Leland, J. O. Polazzi and R. N. Schut, *ibid.*, **23**, 166 (1980). (b) J. O. Polazzi, R. N. Schut, M. P. Kotick, J. F. Howes, P. F. Osgood, R. K. Razdan and J. E. Villarreal, *ibid.*, **23**, 174 (1980).

(4) W. King, W. G. Penprasse and M. C. Kloetzel, *J. Org. Chem.*, **26**, 3558 (1961).

(5) H. Tada, M. Kobayashi and Y. K. Sawa, *Tetrahedron Letters*, 1805 (1969).

(6) U. Weiss, *J. Org. Chem.*, **22**, 1505 (1957).

(7) H. Rapoport, C. H. Lovell, H. R. Reist and M. E. Warren, *J. Am. Chem. Soc.*, **89**, 1942 (1967).

(9) R. B. Barker and H. Rapoport, *J. Med. Chem.*, **19**, 1175 (1976).
(9) I. Belsky, *J. Chem. Soc., Chem. Commun.*, 237 (1977).
(10) J. W. Lewis, K. W. Bentley and A. Cowan, *Annu. Rev. Pharmacol.*, **11**, 241 (1971).
(11) H. C. Brown, E. F. Knights and C. G. Scouten, *J. Am. Chem. Soc.*, **96**, 7765 (1974).
(12) S. L. Huang, K. Omura and D. Swern, *J. Org. Chem.*, **41**, 3329 (1976).
(13) L. F. Fieser and M. Fieser, "Reagents for Organic Synthesis", Vol. 1, John Wiley and Sons, New York, NY, 1967, p. 812.
(14) W. J. Middleton, *J. Org. Chem.*, **40**, 574 (1975); M. Sharma and W. Korytnyk, *Tetrahedron Letters*, 573 (1977); R. A. Sharma, I. Kavai, Y. L. Fu and M. Bobek, *ibid.*, 3433 (1977).
(15) T. J. Tewson and M. J. Welch, *J. Org. Chem.*, **43**, 1090 (1978).
(16) B. A. Whittle, *Br. J. Pharmacol.*, **22**, 246 (1964).