Investigation of the Grewe Codeine Method. Attempts to Achieve a Practical Synthesis

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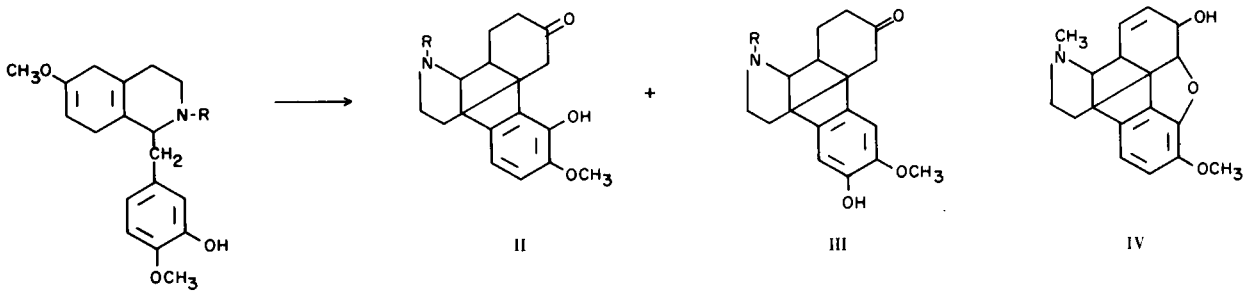
The svnthesis of 1-(2′-bromo-4′-methoxy-5′-hydroxybenzyl)-6-keto-Δ^{4a-5}-decahydroisoquinoline (IX) is described. Efforts to cyclize this intermediate or its *N*-acyl derivatives in acidic media to morphinan products were unsuccessful. The presence of the *para*-bromine blocking group apparently exerts a deactivating influence on the phenolic ring. 1-(3′,5′-Dihydroxy-4′-methoxy-benzyl)-6-methoxy-1,2,3,4,5,8-hexahydroisoquinoline (XVIII) was readily cyclized to 2-hydroxydihydronorthebainone. However, attempts to remove the 2-hydroxy group and subsequent conversion to dihydronorcodeine were unrewarding.

In 1967, Grewe and co-workers (1,2) announced a new synthesis of codeine based on preparation of dihydrothebainone (IIa), previously shown to be convertible to codeine (3) (IV). The key step in the synthesis was the acid catalyzed hydrolysis and cyclization of the hexahydroisoquinoline intermediate (Ia) to dihydrothebainone. However a major difficulty was the low yield (*ca.* 3%) of the desired product (IIa) accompanied by about 40% of the isomer (IIIa) resulting from *para*-oriented morphinan ring closure. A variety of other *N*-substituted intermediates (Ic) gave similar results, however, less severe conditions could be utilized for cyclization of the *N*-acyl compounds.

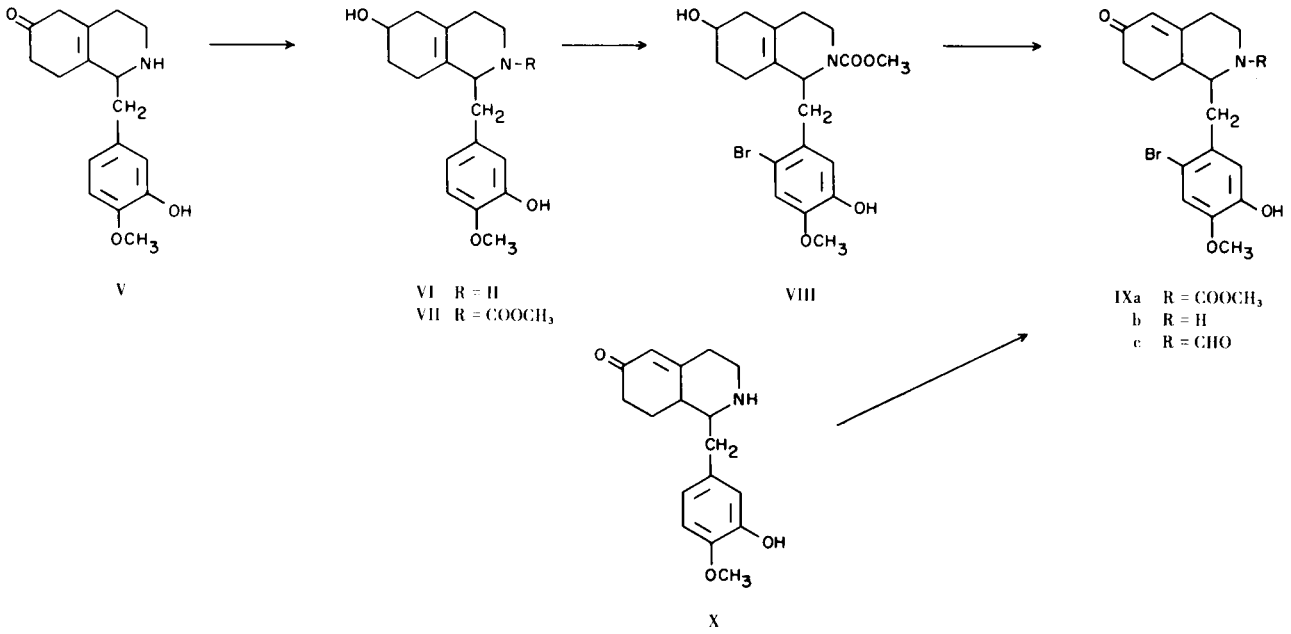
The process pioneered by Grewe still offered an attractive method for a practical synthesis of codeine. We sought to improve the yields in this sequence by incorporation of a bromine atom para to the phenolic hydroxyl to prevent formation of the undesired isomer during ring closure. It was envisioned that the bromine blocking atom could be removed by reduction with lithium aluminum hydride, which would also serve to convert a suitable *N*-acyl substituent (N-CHO or $COOCH_3$) to the required N-CH_3 in codeine. The method of Gates and Tschudi (3) for conversion of 1-bromo codeinone to codeine involves such a reductive removal of this aromatic bromine.

Our initial approach began with the ketone (V) (1) which was reduced by sodium borohydride in 72% yield to the alcohol (VI). Treatment of VI with an excess of methyl chloroformate in alkali followed by saponification of carbonate esters yielded the *N*-carbomethoxy diol (VII) as a foam. Treatment of VII with bromine in chloroform gave selective bromination of the aromatic ring to afford VIII (crystalline) in a 75% yield. Oppenauer oxidation of VIII (cyclohexanone-aluminum-*t*-butoxide) gave the bromo-*N*-carbomethoxy enone (IXa), whose structure was confirmed by elemental, infrared and nmr analyses.

Several attempts were made to cyclize IXa to a morphi-



Ia, R = CH_3
b, R = H
c, R = $COOCH_3$, CHO, CH_3, CO

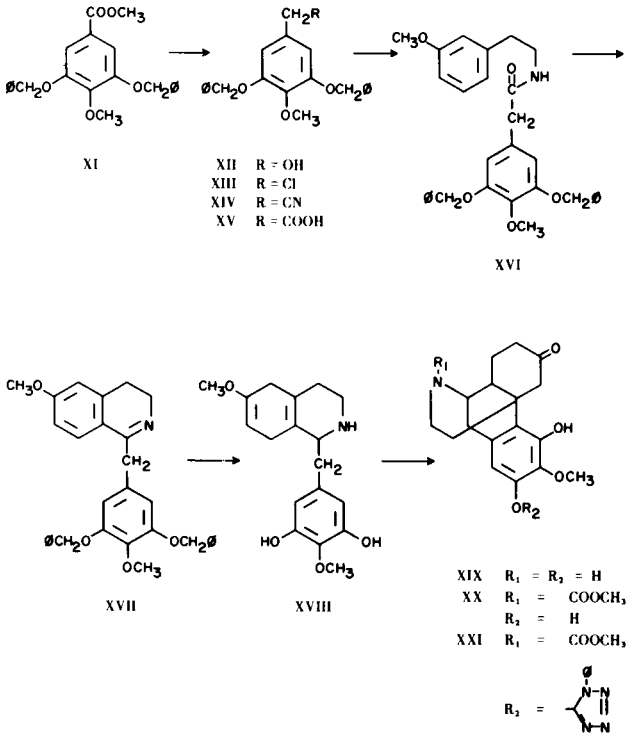


nan structure under a variety of acidic conditions. Infrared spectra were examined for presence of unconjugated ketone while nmr spectra were monitored for loss of an aromatic proton. However, no evidence of ring closure was obtained. It was formally possible that IXa having been formed in alkaline media, might possess the opposite stereochemistry at the ring juncture, which would make ring closure difficult and afford the unnatural epimer at C-14. Bromination of X (acid formed juncture) afforded the bromo enone (IXb). The NH was blocked with N-$COOCH_3$ *via* treatment of IXb with methyl chloroformate followed by brief alkaline hydrolysis of *O*-carbonate. The product was non-crystalline, but gave an infrared spectrum and tlc very similar to IXa obtained by Oppenauer oxidation. In addition the N-CHO derivative (IXc) was prepared by reaction of IXb with ethyl formate at 100°. Neither IXb or c or the N-$COOCH_3$ derivative could be cyclized with acid to afford morphinan products (4). This is apparently due to serious deactivation of the aromatic ring by bromine. A similar cyclization where methyl was used as a *para* blocking group was successful (5), indicating that sufficient electron density is available *ortho* to the phenolic group in the absence of electron withdrawing substituents.

An alternate route designed to proceed *via* the intermediate 2-hydroxy-dihydronorthebainone (XIX) was also investigated. Reduction of methyl 3,5-dibenzyloxy-4-methoxybenzoate (XI) (6) with lithium aluminum hydride yielded the benzyl alcohol (XII). Treatment with hydrogen chloride in benzene gave the chloride (XIII) in 98% yield. Direct treatment of XIII with sodium cyanide in DMSO afforded the nitrile (XIV) in quantitative yield. Alkaline hydrolysis of XIV gave the acid (XV) which was coupled with an equivalent of 3-methoxyphenethylamine by reflux in xylene with water separation to afford the amide (XVI). Bischler-Napieralski cyclization with phosphorus pentachloride in chloroform at room temperature gave the syrupy dihydroisoquinoline (XVII), characterized as the methiodide salt.

Birch reduction of XVII with excess lithium in liquid ammonia yielded the desired hexahydroisoquinoline (XVIII). This intermediate was refluxed with concentrated hydrochloric acid for 6 hours which readily effected hydrolysis and cyclization to the 2-hydroxydihydronorthebainone (XIX). The material was characterized as the picrate and also transformed to the hydrochloride salt by exchange with Dowex 2 (Cl^-) resin. Infrared spectra (Nujol) of both salts showed saturated ketone at 5.87 μ, (7) while the nmr spectrum of the hydrochloride salt (d_6-DMSO) clearly showed only one remaining aromatic proton. Conversion of XIX to the N-$COOCH_3$ derivative (XX) gave a crystalline product whose infrared spectrum showed saturated C=O at 5.83 μ and urethane at 5.95 μ.

Attempts to deoxygenate XX *via* preparation of a 5-phenyl-1-tetrazole ether (presumably on the less hindered 2-OH) to be followed by hydrogenolysis (8) to *N*-carbomethoxydihydronorthebainone were unsuccessful. A non-crystalline, but chromatographically homogeneous phenyl tetrazole ether (regarded as XXI) was obtained, but was unaffected by exposure to hydrogen. Similarly attempts to brominate alpha to the ketone in XIX or XX and effect alkaline closure of the oxide bridge gave intractible products. Oxidative instability and the low yields generally obtained in this alternate series discouraged further exploration.



EXPERIMENTAL

1-(3′-Hydroxy-4′-methoxybenzyl)-6-hydroxy-1,2,3,4,5,6,7,8-octahydroisoquinoline (VI).

A mixture of 18.4 g. of ketone (V) (1), 410 ml. of ethanol and 5.2 g. of sodium borohydride was stirred 3.5 hours, at room temperature. The solvent was removed *in vacuo* and the residue treated with 150 ml. of water. The *p*H was adjusted to 9-10 with acetic acid and the crystalline precipitate was collected and dried to leave 13.2 g. (72%). Recrystallization of a portion from methanol afforded an analytical sample, m.p. 195-198°.

Anal. Calcd. for $C_{17}H_{23}NO_3$: C, 70.6; H, 8.01; N, 4.84. Found: C, 70.3; H, 7.83; N, 5.01.

1-(3′-Hydroxy-4′-methoxybenzyl)-2-carbomethoxy-6-hydroxy-1,2,3,4,5,6,7,8-octahydroisoquinoline (VII).

A mixture of 11.2 g. of the amino diol (VI), 168 ml. of 10% sodium hydroxide and 110 ml. of acetone was chilled to 0-5° and treated dropwise with 2.0 ml. of methyl chloroformate. The mixture was stirred 1.5 hours at 0-5° and diluted with 550 ml. of water. The solid was collected and heated at 60° with 360 ml. of 1*N* sodium hydroxide in 140 ml. of methanol for 2 hours. The solution was diluted with 600 ml. of water, adjusted to *p*H 7 with acetic acid and extracted thrice with 250 ml. portions of chloroform. The extract was dried (magnesium sulfate) and evaporated *in vacuo* to leave 11.8 g. of a foamy residue. The infrared spectrum showed strong OH (3.0) and N-$COOCH_3$ (5.9-6.0) and *no* -O-$COOCH_3$ bands.

1-(2′-Bromo-4′-methoxy-5′-hydroxybenzyl)-2-carbomethoxy-6-hydroxy-1,2,3,4,5,6,7,8-octahydoisoquinoline (VIII).

To a solution of 3.9 g. (10.4 mmoles) of the diol urethane (VII) in 50 ml. of chloroform was added, dropwise with stirring, 0.54 ml. (10.5 mmoles) of bromine in 20 ml. of chloroform. After 5 minutes the solution was washed with 60 ml. of saturated bicarbonate. The organic phase was dried (magnesium sulfate) and evaporated *in vacuo* to leave a foamy residue. Crystallization from aqueous 2-propanol afforded 3.3 g. (75%) in two crops which showed only a trace contaminant in thin layer chromatography(silica gel, ethyl acetate). Material from another run was recrystallized from methanol to afford white crystals, m.p. 179.5-181.5°.

Anal. Calcd. for $C_{19}H_{24}BrNO_5$: C, 53.6; H, 5.68; Br, 18.7. Found: C, 54.3; H, 5.82; Br, 18.4.

1-(2′-Bromo-4′-methoxy-5′-hydroxybenzyl)-2-carbomethoxy-6-keto-$\Delta^{4a,5}$-decahydroisoquinoline (IXa).

A mixture of 1.50 g. of the bromo alcohol (VIII), 7.3 ml. of cyclohexanone and 100 ml. of toluene was heated to boiling and 30 ml. of toluene distilled to dry the system. Aluminum *t*-butoxide (1.72 g.) in 25 ml. of toluene was added and the mixture refluxed for 4 hours. The solvent was removed *in vacuo* and the residue treated with 25 ml. of 1*N* hydrochloric acid. The mixture was extracted with chloroform and the extract dried and evaporated to leave a gummy residue. The gum was twice washed with petroleum and dried to leave 1.3 g. The material was chromatographed on 110 g. of silica gel with elution by chloroform ethyl acetate (1:1). The slower moving of two components afforded crystalline material. Recrystallization from benzene-cyclohexane gave an analytical sample, m.p. 148-151°; ir: 3.20 (phenolic OH), 5.84 (N-$COOCH_3$), 6.00 (cong. C=O); nmr (100 m.c.) (τ): 3.05 (1H), 3.32 (1H), aromatic, 4.46 (1H) olefin, 6.20 (3H) $ArOCH_3$.

Anal. Calcd. for $C_{19}H_{22}BrNO_5$: C, 53.8; H, 5.23; N, 3.30; Br, 18.8. Found: C, 53.7; H, 5.37; N, 3.41; Br, 18.5.

1-(2′-Bromo-4′-methoxy-5′-hydroxybenzyl)-6-keto-$\Delta^{4a,5}$-decahydroisoquinoline (IXb).

The conjugated ketone (X) (9), 3.20 g. was dissolved in 80 ml. of acetic acid and a solution of 0.64 ml. of bromine in 10 ml. of acetic acid was added dropwise. The mixture was stirred for 20 minutes and evaporated *in vacuo*. The residue was dissolved in 80 ml. of water and the *p*H adjusted to 8 with 1*N* sodium hydroxide. The yellow precipitate was collected and dried to leave 4.4 g. Trituration with hot 2-propanol afforded 1.81 g. (44%) of tan crystals. An analytical sample m.p. 204-209° was obtained from another run; ir: 5.99 μ (conj. C=O); nmr (τ): 2.96 (1H) Ar, 3.18 (1H) Ar, 4.22 (1H) olefin, 6.26 (3H) $ArOCH_3$,

Anal. Calcd. for $C_{17}H_{20}BrNO_3$: C, 55.7; H, 5.50; Br, 21.8; N, 3.83. Found: C, 55.6; H, 5.69; Br, 21.7; N, 3.73.

1-(2′-Bromo-4′-methoxy-5′-hydroxybenzyl)-2-formyl-6-keto-$\Delta^{4a,5}$-decahydroisoquinoline (IXc).

A solution of 290 mg. of IXb in 8 ml. of ethyl formate was heated at 135-140° in a Parr bomb for 5 hours. The solvent was evaporated and the residual syrup partitioned between chloroform and 1*N* hydrochloric acid. The chloroform extract was dried and evaporated to leave 251 mg. (81%) of a yellow foam; ir: 3.10 (OH) 6.00 (N-CHO, conj. C=O).

Morphinan Ring Closure Attempts.

Compounds IXa-c and X were especially investigated with regard to cyclization to a morphinan system. Infrared spectra were examined for presence of unconjugated ketone while nmr spectra were monitored for loss of an aromatic proton. Compound X which was unbrominated in the aromatic ring gave either no reaction or the *para* oriented product (IIIa) as reported by Grewe. Compounds IXa-c afforded no detectable amounts of cyclized products under the conditions outlined below.

Compound IXa.

Sulfuric acid-ether (3:2), 25-50°, 20-60 hours, boron trifluoride-etherate, 25°, 24 hours; thallous ethoxide-ethanol, 80°; xylene-sulfur-

ic acid, 140°, 20 hours; sunlight 5 days; polyphosphoric acid, 80° and 120°, 20 hours.

Compound IXb.

Eighty five percent phosphoric acid, 120°, 3-20 hours; polyphosphoric acid, 90-120°, 3-16 hours. 3*N* and 6*N* hydrochloric acid, 17 hours, 80-100°; sulfuric-acetic acids, 90°, 40 hours; phosphoryl chloride-benzene, 80°, 15 hours; potassium hydroxide-methanol, 65°, 24 hours.

Compound IXc.

Sulfuric acid-ether (3:2), 25-80°, hours, polyphosphoric acid, 100°, 15 hours.

In a separate experiment IXb was treated with methyl chloroformate and 10% sodium hydroxide in acetone and the intermediate *N,O*-carbonate was saponified with 1*N* sodium hydroxide in methanol at room temperature for 30 minutes. The gummy product refused to crystallize, but spectral and tlc properties were very similar to IXa. Treatment with 80% sulfuric acid-ether (3:2) for 24 hours at room temperature was without effect.

3,5-Dibenzyloxy-4-methoxybenzyl Alcohol (XII).

To an ice cold suspension of 18.0 g. of lithium aluminum hydride in 1300 ml. of ether was added 89.0 g. of the solid ester (XI) (6) over 10 minutes with stirring. The thick mixture was dept at 0-5° for 30 minutes and then refluxed 3.5 hours. The mixture was cooled in ice and decomposed by the slow addition of ice water, after which the ether was decanted from the precipitated salts. The residue was extracted twice with 500 ml. portions of dichloromethane. The combined extracts of this and an identical companion run were dried and evaporated to leave 136 g. (83%) of white crystals, devoid of carbonyl bands in the infrared. A portion was recrystallized from benzene to yield an analytical sample, m.p. 105-106°.

Anal. Calcd. for $C_{22}H_{22}O_4$: C, 75.4; H, 6.33. Found: C, 75.5; H, 6.35.

3,5-Dibenzyloxy-4-methoxybenzyl Chloride (XIII).

A stirred mixture of 16.0 g. of the alcohol (XII) and 100 ml. of benzene was cooled in an ice bath while hydrogen chloride was introduced. After 15 minutes complete solution occurred and gassing was stopped. After 3 hours at room temperature an aqueous layer had settled. The benzene phase was separated and evaporated *in vacuo* to leave 16.5 g. (98%) of crystalline residue ir: *no* OH at 3.0 or 9.5 μ.

3,5-Dibenzyloxy-4-methoxybenzyl Cyanide (XIV).

A mixture of 1.0 g. of sodium cyanide, 15 ml. of dimethyl sulfoxide and 5.0 g. of the chloride (XIII) was warmed to give a solution, which was dept at ambient temperature for 20 hours. After dilution with 120 ml. of ice water the precipitated solid was collected, washed with water and dried to leave 4.86 g. (100%) of white crystals, which were homogeneous on thin layer chromatograms and possessed a 4.50 μ band in the infrared. Recrystallation from benzene-hexane (1:1) afforded an analytical sample, m.p. 92-93.5°.

Anal. Calcd. for $C_{23}H_{21}NO_3$: C, 76.9; H, 5.89; N, 3.90. Found: C, 77.0; H, 5.92; N, 3.85.

3,5-Dibenzyloxy-4-methoxyphenylacetic Acid (XV).

A mixture of 16.0 g. of the nitrile (XIV), 190 ml. of 10% sodium hydroxide and 80 ml. of 2-methoxyethanol was stirred at reflux 6 hours. After dilution with 1200 ml. of water, the resulting solution was washed with 100 ml. of ether and acidified with 6*N* hydrochloric acid to precipitate the acid. The crystals were collected, washed with water and dried to leave 14.0 g. (87%), m.p. 138-140°; lit. (6) m.p. 138-139°.

N-m-Methoxyphenethyl-3,5-dibenzyloxy-4-methoxyphenylacetamide (XVI).

A mixture of 10.0 g. of the acid (XV), 4.0 g. of 3-methoxyphenethylamine and 27 ml. of xylene was refluxed with water separation for 4 hours. The solution was diluted with 27 ml. of cyclohexane and after 2 hours the crystals were collected, washed with cyclohexane and dried to leave 10.0 g. (74%). Recrystallization from benzene-cyclohexane (8:5) afforded an analytical sample, m.p. 79-80.5°.

Anal. Calcd. for $C_{32}H_{33}NO_5$: C, 75.1; H, 6.50; N, 2.74. Found: C, 75.1; H, 6.47; N, 2.69.

1-(3′,5′-Dibenzyloxy-4′-methoxybenzyl)-6-methoxy-3,4-dihydroisoquinoline (XVII).

To an ice cold, stirred suspension of 0.63 g. (0.003 mole) of phosphorus pentachloride in 3 ml. of chloroform was slowly added 1.02 g. (0.002 mole) of the amide (XVI). The mixture was stirred 1 hour at 0-5° and 22 hours at room temperature. The solvent was removed *in vacuo* and the yellow gum stirred with ice water and ether for 1 hour. The liquid portion was decanted and the residual gum was alkalized with 10% sodium hydroxide and extracted with ether. The ether extract was dried (magnesium sulfate) and evaporated to leave 0.80 g. of yellow syrup whose infrared spectrum showed loss of the amide bands.

The syrup (0.70 g.) was dissolved in 3 ml. of methyl iodide and after 40 minutes the solution was diluted with excess ether to give a gummy crystalline precipitate. The solvent was decanted and the residue warmed with 10 ml. of ethanol for 15 minutes. After another hour the white crystals were collected, washed with ethanol and dried to leave 0.50 g. of the methiodide salt, m.p. 171-173°.

Anal. Calcd. for $C_{33}H_{34}INO_4$: C, 62.5; H, 5.40; N, 2.21. Found: C, 62.4; H, 5.47; N, 2.12.

1-(3′,5′-Dihydroxy-4′-methoxybenzyl)-6-methoxy-1,2,3,4,5,8-hexahydroisoquinoline (XVIII).

To a stirred suspension of 6.9 g. of lithium in 300 ml. of liquid ammonia at -70° was added 10.0 g. of the dibenzyloxy compound (XVII) in 100 ml. of tetrahydrofuran over 30 minutes. The bronze-blue mixture was stirred at the reflux temperature of ammonia for 2 hours, when 55 ml. of methanol was added dropwise over 35 minutes. The ammonia was evaporated under nitrogen and the residue dissolved in 300 ml. of ice water. Ammonium chloride (80 g.) was added in portions at 0-5° with stirring. The dark mixture was extracted with 100 ml. and three 50 ml. portions of chloroform. The extract was dried (magnesium sulfate) and evaporated *in vacuo* to leave 7.5 g. of partially crystalline, brown residue. Trituration with 13 ml. of methanol afforded 3.30 g. (51%) of tan crystals; ir: 3.0 μ (OH), 3.9 (NH_2^+), 5.90, 6.00 (dihydroanisole). A portion was treated with warm methanol to afford white crystals, m.p. 198-204° dec.

Anal. Calcd. for $C_{18}H_{23}NO_4 \cdot \frac{1}{2}H_2O$: C, 66.3; H, 7.42; N, 4.29. Found: C, 66.2; H, 7.23; N, 4.13.

2-Hydroxydihydronorthebainone (XIX).

A mixture of 2.0 g. of the enol ether (XVIII) and 30 ml. of concentrated hydrochloric acid was refluxed 6 hours and evaporated *in vacuo*. The dark syrup was dissolved in 10 ml. of water and added to 150 ml. of 1% picric acid solution to give a crystalline precipitate. The solid was collected, washed with water and dried to leave 2.30 g. (67%) of picrate. The crude material was digested with 12 ml. of warm ethanol cooled and the crystals collected to yield 1.40 g. of yellow crystals m.p. 162-164°.

Anal. Calcd. for $C_{23}H_{24}N_4O_{11} \cdot 1.5H_2O$: C, 49.4; H, 4.87; N, 10.0. Found: C, 49.3; H, 4.54; N, 9.90.

The picrate was converted to the hydrochloride salt by stirring with excess Dowex 2 (Cl^-) resin in warm 90% methanol. The salt was obtained as a foam. Infrared spectra of the picrate and hydrochloride showed strong non-conjugated ketone bands at 5.87 μ. The nmr spectrum of the hydrochloride in d_6-DMSO clearly showed only one aromatic proton at 3.80 τ along with 0.54 (2H, NH_2^+) and 6.52 (3H, OCH_3) as readilty assignable signals.

N-Carbomethoxy-2-hydroxydihydronorthebainone (XX).

To an ice cold solution of 3.6 g. of XIX as the hydrochloride salt in 20 ml. of water was added 50 ml. of 10% sodium hydroxide under a nitrogen atmosphere. Then at 0-5° was added 6.0 ml. of methyl chloroformate over 5 minutes and the mixture was stirred for 2.5 hours at 0-5°. Ice water (100 ml.) was added, followed by acidification (6*N* hydrochloric acid to *p*H 2) and extraction with two 100-ml. portions of chloroform. The chloroform was washed with 25 ml. of water, dried (magnesium sulfate) and evaporated to leave 3.5 g. of dark foam. The crude N,O-carbonate was heated at 60° in a mixture of 30 ml. of methanol -75 ml. of 1*N* sodium hydroxide. The mixture was cooled in ice, diluted to 200 ml. with ice water and acidified to *p*H 2. The product was extracted into two 75-ml. portions of chloroform, dried over magnesium sulfate and evaporated to leave 2.5 g. of amber foam. Trituration with acetone afforded 171 mg. of beige colored crystals, m.p. 209-212°. The infrared spectrum (Nujol) was very sharp and showed OH (3.15 μ), ketone (5.83) and urethane (5.95).

Anal. Calcd. for $C_{19}H_{23}NO_6$: C, 63.1; H, 6.42; N, 3.88. Found: C, 63.1; H, 6.49; N, 4.04.

N-Carbomethoxy-2-(5-phenyl-1-tetrazolyloxy)dihydronorcodeinone (XXI).

A mixture of 1.16 g. of the hydroxy ketone (XX), 0.96 g. of 1-chloro-5-phenyltetrazole, 0.96 g. of potassium carbonate and 20 ml. of acetone was stirred at reflux 20 hours under nitrogen. The solvent was removed and the residue partitioned between chloroform and water. The chloroform extract was evaporated and the residue chromatographed on 50 g. of silica gel. Elution with ethyl acetate afforded 450 mg. of foamy solid. The infrared spectrum was free of chlorotetrazole reagent and showed a prominent 6.5 μ band characteristic of the tetrazolyl ethers (-C=N). Attempts to obtain crystalline material suitable for analysis were unsuccessful.

Hydrogenations of the apparent tetrazolyl ether (XXI) over 5% Pd/C or palladium black in ethanol were without effect. The tetrazole ether of p-phenylphenol was readily split to yield biphenyl and 5-phenyl-1-tetrazolone.

Acknowledgment.

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(4) In a patent, Netherlands 7,107,921, December 13, 1971 (Merck and Co., Inc.), the preparation of IXa, b, and c is claimed via route similar to ours. It was also claimed that cyclization of IXa or c occurs readily with 80% sulfuric acid-ether (1:1) at room temperature to yield IIc products, contrary to our observation. No evidence was presented to show that the claimed intermediates were ever obtained.

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