[CONTRIBUTION FROM THE COBB CHEMICAL LABORATORY, UNIVERSITY OF VIRGINIA, AND THE NATIONAL INSTITUTE OF HEALTH]

The Aminomorphides and Aminocodides[1]

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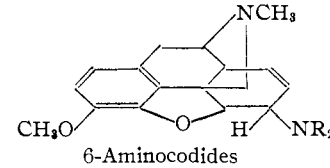
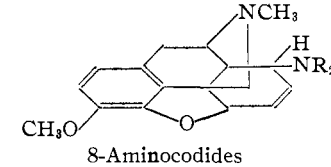
The investigation of compounds derived from the morphine series and carrying basic groups in ring III was begun in the Virginia Laboratory in 1934, with the object of determining the effect of such basic radicals upon physiological action. As early as 1903, Vongerichten and Müller[3] found that α-chlorocodide entered into reaction with piperidine to yield a dibasic compound in which the piperidino group was assumed to have taken the place of the chlorine atom of α-chlorocodide. Some years later, Wieland and Kappelmeier[4] carried out the parallel reaction between α-chloromorphide and diethylamine (diethylaminomorphide), as did von Braun and Kindler[5] with α-chlorocodide and dimethylamine and diethylamine.

As is now well known, replacement of the halogen atom in the halogenomorphides or halogenocodides by other groups may involve both configurational and positional changes, as exemplified in the hydrolysis of these halogeno compounds to α-, β- and γ-isomorphines, or to the corresponding codeine isomers. Before significant conclusions concerning structure and physiological action can be drawn, it is therefore necessary to scrutinize the structural evidence for any derivative originating from replacement of a halogen atom (or perhaps other groups) in ring III of the morphine series.

There exist, to our knowledge, no distinctive physical or chemical criteria that may be applied to the determination of the configuration of groups at C-6 or C-8 relative to any arbitrarily chosen standard. We have, in the past, classified certain derivatives as having the codeine or isocodeine, the pseudocodeine or allopseudocodeine configuration, on the basis of similarities in pharmacological action,[6] with full realization, however, of the limitations and weaknesses of such deductions. In respect to positional differences, between the unsaturated 6- and 8-substituted types, we possess, in catalytic hydrogenation, a determinative method that has been in agreement with so many compounds of proved structure that it probably may be considered reliable as far as the morphine series is concerned. Namely, for all those derivatives having the substituent (or hydrogen) in the 8-position, and a double bond at the 6,7-position, the usual course taken by hydrogenation results in opening the oxygen bridge simultaneously with, or before, saturation of the double bond. The derivatives with the 6-substituent (halogen excepted) and the 7,8-double bond undergo hydrogenation normally, without involving the oxygen bridge.



6-Aminocodides



8-Aminocodides

As would be expected from observations already reported in the thiocodide and other series, two of the examples cited, reactions of α-chlorocodide with piperidine and of α-chloromorphide with diethylamine, result, respectively, in 8-piperidocodide and 8-diethylaminomorphide. There can be little doubt that the dimethylaminocodide of von Braun and Kindler also carries the new basic group in the 8-position. The reaction product from α-chlorocodide and piperidine, 8-piperidocodide, under the ordinary conditions of hydrogenation, takes up two moles of hydrogen, to give the tetrahydro derivative, in which not only has the alicyclic double bond been saturated, but the

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(3) Vongerichten and Müller, *Ber.*, **36**, 1590 (1903).

(4) Wieland and Kappelmeier, *Ann.*, **382**, 306 (1911).

(5) Von Braun and Kindler, *Ber.*, **49**, 2655 (1916).

(6) "Studies on Drug Addiction," Supplement No. 138 to the Public Health Reports, Washington, 1938, p. 15. Lutz and Small. "Reduction Studies in the Morphine Series," IX, *J. Org. Chem.*, in press.

cyclic ether group been opened reductively as well. As with other examples of 6,7-unsaturated morphine types,[7] 8-piperidocodide, under special hydrogenation conditions, can be converted in part to the non-phenolic "normal" dihydro derivative. The latter, no longer possessing the pseudocodeine type of unsaturated system, is indifferent toward further reduction.

By the reaction of α-chloromorphide with piperidine, the analogous 8-piperidomorphide is obtained, whose relationship to the known 8-piperidocodide can be shown by methylation. 8-Piperidomorphide, like its methyl ether, absorbs two moles of hydrogen readily, to yield the corresponding diphenolic tetrahydro derivative. Although reduction of the hydrochloride in glacial acetic acid resulted in diminished hydrogen absorption, the desired dihydro derivative was not isolated in pure form.

We have verified the Wieland and Kappelmeier reaction of diethylamine with α-chloromorphide, to form a diethylaminomorphide, but because of the more favorable solubility of the codides, and their greater stability toward oxidation, turned our attention to the 8-diethylaminocodide of von Braun and Kindler. As a pseudocodeine type, this undergoes reduction with additon of two moles of hydrogen, to give tetrahydro-8-diethylaminocodide, so that the 8-position for the basic group seems assured.

α-Chlorocodide also reacts with liquid ammonia at about 50°, with substitution of an amino group at the 8-position and loss of the 6-halogen atom. 8-Aminocodide, as a primary amine, undergoes acetylation readily with cold acetic anhydride to yield 8-diacetylaminocodide. 8-Aminocodide behaves in a typical way toward catalytic reduction. As hydrochloride, in glacial acetic acid, it can be reduced to a non-phenolic dihydro derivative. As base, in alcohol, on the other hand, it takes up two moles of hydrogen, giving the phenolic tetrahydro-8-aminocodide.

All of the products that we have examined derived from amination of α-chloromorphide or α-chlorocodide, appear to have resulted from an α,γ-shift, and carry the basic group in the 8-position. The halogeno compounds of the morphine series that are generally believed to carry the halogen atom at the 8-position, namely, bromocodide and bromomorphide, and β-chlorocodide and β-chloromorphide, seem to react with amino compounds with the reverse α,γ-shift, to yield the 6-amino derivatives. Bromomorphide and piperidine, at 100°, give 6-piperidomorphide. We believe the assignment of the 6-position to the substituent to be justified from the fact that the compound cannot be induced to take up more than one mole of hydrogen, and yields only a dihydro derivative. 6-Piperidomorphide undergoes methylation to give 6-piperidocodide, a compound that also results from the action of piperidine with either bromocodide or β-chlorocodide. 6-Piperidocodide likewise is saturated by addition of one mole of hydrogen, although the reduction product was so difficult to purify that analytical data cannot be advanced.

The identity of the amination products from bromocodide and β-chlorocodide lends additional support to the conception that both of these compounds carry the halogen atom in the 8-position. It is remarkable that while the reactions of the α-halogeno types, and of β-chlorocodide and bromocodide, with piperidine seemed to proceed with equal facility, bromocodide was regained quite unchanged from attempted reaction with liquid ammonia. 6-Aminocodide will perhaps be obtained when facilities for working at higher temperatures and pressures are available. The failure with bromocodide is the more unexpected in view of the fact that the bromo base seems to enter into replacement reactions with hydriodic acid and with mercaptans as readily as does α-chlorocodide, in contrast to the inactive β-chloro series.

The aminocodides and aminomorphides are outstanding exceptions to the general rule that replacement of the alcoholic hydroxyl of the morphine types by other groups leads to increased physiological activity. Introduction of the basic group usually reduced toxicity, and greatly decreased analgesic action.[8] We have observed that the substitution of a basic group in the aromatic ring of morphine (2-aminomorphine[4,9]) also results in a great diminution of physiological action. The intramolecular acidic and basic relationship in the morphine types appears to be intimately associated with biological effect.

Experimental

8-Diethylaminomorphide.—This base was prepared essentially according to the procedure of Wieland and Kap-

(7) Small and co-workers, THIS JOURNAL, **54**, 4715 (1932); **56**, 2466 (1934); **57**, 364 (1935); **56**, 1928 (1934); **57**, 361 (1935); *J. Org. Chem.*, **1**, 194 (1936); THIS JOURNAL, **57**, 2651 (1935); **55**, 2874 (1933).

(8) "Studies on Drug Addiction," pp. 21, 24.

(9) Ochiai and Nakamura, *Ber.*, **72**, 684 (1939).

pelmeier. After three sublimations in a high vacuum, it had the melting point 201–204° (evac. tube) and $(\alpha)^{21}D$ +49.1° (methanol, *c*, 0.87) (W. and K. observed the melting point 203°).

Anal. Calcd. for $C_{21}H_{28}N_2O_2$: N, 8.2. Found: N, 8.1.

On treatment with diazomethane it yielded 8-diethylaminocodide. 8-Diethylaminomorphide dihydriodide was prepared in the usual way and purified from water; m. p. 87–93° (evac. tube), $(\alpha)^{25}D$ +2.6° (water, *c*, 0.38). The salt appears to be a sesquihydrate.

Anal. Calcd. for $C_{21}H_{30}I_2N_2O_2 + 1.5H_2O$: I, 40.8; H_2O, 4.3. Found: I, 41.1; H_2O, 4.6.

The diperchlorate was crystallized from water, m. p. 114–116° (evac. tube), $(\alpha)^{19}D$ +4.4° (water, *c*, 0.91).

Anal. Calcd. for $C_{21}H_{30}Cl_2N_2O_{10}$: Cl, 13.1. Found: Cl, 13.5.

8-Piperidomorphide.—Ten grams of α-chloromorphide with 10 g. of piperidine was heated in an evacuated sealed tube at 100° for thirty minutes. The product was dissolved in 3 *N* hydrochloric acid, precipitated with excess of sodium carbonate and the precipitate extracted into ether. The yield of crystalline product was 9.2 g. It was purified from alcohol and sublimed in a high vacuum at 200°; m. p. 222–224° (evac. tube), $(\alpha)^{24}D$ +28.7° (methanol, *c*, 1.15).

Anal. Calcd. for $C_{22}H_{28}N_2O_2$: C, 74.9; H, 8.0; N, 7.9. Found: C, 74.9; H, 7.8; N, 8.2.

The dihydriodide was prepared in 10% acetic acid with potassium iodide, redissolved in dilute acetic acid and again precipitated with potassium iodide. It was purified from water and had $(\alpha)^{23}D$ +14.9° (water, *c*, 0.37), m. p. 208–214° (evac. tube).

Anal. Calcd. for $C_{22}H_{30}I_2N_2O_2$: I, 41.7. Found: I, 42.3.

The monomethiodide was prepared in methanol solution, and purified from water; m. p. 243–245° (evac. tube), $(\alpha)^{23}D$ +23.7° (50 vol. % alcohol, *c*, 1.14).

Anal. Calcd. for $C_{23}H_{31}IN_2O_2$: I, 26.4. Found: I, 25.8.

Tetrahydro-8-piperidomorphide.—Two grams of 8-piperidomorphide in 30 cc. of 5% acetic acid with 50 mg. of platinum oxide absorbed two moles of hydrogen rapidly. The new base was isolated with sodium carbonate and ether and was sublimed three times in a high vacuum. It had the m. p. 270–280° (evac. tube, dec.) and $(\alpha)^{26}D$ +45.1° (10% acetic acid, *c*, 0.63). The ferric chloride test was moss-green. No crystalline salts could be obtained.

Anal. Calcd. for $C_{22}H_{32}N_2O_2$: C, 74.1; H, 9.0; N, 7.9. Found: C, 73.8; H, 8.9; N, 8.1.

Acetylation with acetic anhydride resulted in a base of m. p. 172–178°.

8-Diethylaminocodide.—This compound, prepared according to von Braun and Kindler and sublimed three times in a high vacuum, had the m. p. 101–103° (von B. and K., 102°) and $(\alpha)^{23}D$ +42.6° (methanol, *c*, 1.0). The same compound was obtained from the methylation of the 8-diethylaminomorphide described above.

The diperchlorate was prepared in dilute perchloric acid in the presence of a little alcohol, and purified from water or alcohol; $(\alpha)^{19}D$ +3.3° (water, *c*, 0.92), m. p. 180.5–183°.

Anal. Calcd. for $C_{22}H_{32}Cl_2N_2O_{10}$: Cl, 12.8. Found: Cl, 12.7.

The dihydriodide was prepared in the usual way and recrystallized from water or alcohol to constant rotation, $(\alpha)^{26}D$ +22.9° (absolute alcohol, *c*, 0.39); m. p. 179–182°.

Anal. Calcd. for $C_{22}H_{32}I_2N_2O_2$: I, 41.6. Found: 1, 41.0, 42.3.

Tetrahydro-8-diethylaminocodide.—Two grams of 8-diethylaminocodide in 50 cc. of ethanol with 80 mg. of platinum oxide absorbed two moles of hydrogen in five hours. The residue from evaporation of the alcohol was washed with a little cold ether. This material melted at 116–119° with gas evolution and was probably hydrated. It was sublimed four times in a high vacuum at 130°; m. p. 154–157°, rotation constant at $(\alpha)^{25}D$ +31.5° (methanol, *c*, 0.75).

Anal. Calcd. for $C_{22}H_{34}N_2O_2$: C, 73.7; H, 9.6. Found: C, 73.6; H, 9.5.

The monoperchlorate was prepared in dilute perchloric acid and crystallized by cooling the solution after addition of a drop of alcohol. It was purified from water, $(\alpha)^{26}D$ +18.3° (water, *c*, 0.30); m. p. 234–238° (evac. tube).

Anal. Calcd. for $C_{22}H_{35}ClN_2O_6$: Cl, 7.7. Found: Cl, 8.0.

8-Piperidocodide.—This base, prepared according to Vongerichten and Müller, was purified from methanol and had the m. p. 116–117° (V. and M. observed m. p. 118°). After four sublimations in a high vacuum, the rotation was constant, $(\alpha)^{22}D$ +25.8° (methanol, *c*, 0.89). The same base was obtained by methylation of 8-piperidomorphide with diazomethane.

Anal. Calcd. for $C_{23}H_{30}N_2O_2$: N, 7.7. Found: N, 7.7.

The di-acid sulfate dihydrate was prepared by dissolving the base in 10% sulfuric acid, from which the salt crystallized immediately. It was crystallized twice from 10% sulfuric acid and twice from alcohol, $(\alpha)^{26}D$ +19.8° (water, *c*, 1.46); m. p. 161–163.5° (evac. tube).

Anal. Calcd. for $C_{23}H_{38}N_2O_2S_2 = C_{23}H_{30}O_2N_2 \cdot 2H_2SO_4 \cdot 2H_2O$: SO_4, 32.1; H_2O, 6.0. Found: SO_4, 32.5; H_2O, 5.4.

The monohydriodide was prepared in the usual way and purified from water. It has $(\alpha)^{24}D$ +13.3° (water, *c*, 0.337); m. p. 234–237° (corr., evac. tube).

Anal. Calcd. for $C_{23}H_{31}IN_2O_2$: I, 25.7. Found: I, 27.3.

A homogeneous salt is very difficult to obtain. Other preparations consisted mostly of the dihydriodide (Calcd.: I, 40.8. Found: I, 38.4, 38.6).

For the monomethiodide of V. and M. we observed the value $(\alpha)^{25}D$ +22.0° (water, *c*, 0.86).

The diperchlorate, purified from water, has the m. p. 181–183° and $(\alpha)^{23}D$ +13.2° (50 vol. % alcohol, *c*, 1.02).

Anal. Calcd. for $C_{23}H_{32}Cl_2N_2O_{10}$: Cl, 12.5. Found: Cl, 12.3.

Tetrahydro-8-piperidocodide.—A solution of 2 g. of 8-piperidocodide in 60 cc. of ethanol with 50 mg. of platinum oxide absorbed 2 moles of hydrogen rapidly. The residue from evaporation of the alcohol was washed with

a little cold ether, and the crystals sublimed twice in a high vacuum; m. p. unsharp at about 125°, rotation constant at $(\alpha)^{25}D$ +36.7° (methanol, *c*, 1.07); ferric chloride test, deep emerald-green.

Anal. Calcd. for $C_{23}H_{34}N_2O_2$: C, 74.5; H, 9.3; N, 7.6. Found: C, 74.7; H, 9.1; N, 7.5.

Dihydro-8-piperidocodide.—Three grams of the amorphous powdery hydrochloride, obtained by treating an ethereal solution of 8-piperidocodide with ethereal hydrogen chloride, was dissolved in 50 cc. of glacial acetic acid and hydrogenated in the presence of 150 mg. of platinum oxide. The absorption of hydrogen stopped at 1.6 moles. The filtered solution was diluted with an equal volume of water, made alkaline with ammonia, and the precipitate extracted into ether. The crystalline residue from evaporation of the ether was recrystallized from alcohol, yield 0.95 g., m. p. 164–167°. Two crystallizations from alcohol and two sublimations in a high vacuum yielded a product of melting point 167–169°, $(\alpha)^{23}D$ −1.2° (methanol, *c* 1.68). The ferric chloride test was negative.

Anal. Calcd. for $C_{23}H_{32}N_2O_2$: C, 74.9; H, 8.8; N, 7.6. Found: C, 75.0; H, 9.1; N, 8.0.

From the alcohol mother liquors, 0.46 g. of pure tetrahydro-8-piperidocodide could be isolated.

8-Aminocodide.—Ten grams of α-chlorocodide in 180 g. of liquid ammonia was held at 50° for twenty-four hours. After excess ammonia had evaporated, the residue was dissolved in dilute hydrochloric acid, and the base was precipitated with sodium hydroxide and brought into ether. The amorphous product was dissolved in warm alcohol and the crystalline base precipitated by slow addition of ether. It was converted to the hydrochloride with alcoholic hydrogen chloride, yield 11 g.[10] A solution of the hydrochloride was treated with alkali and extracted rapidly with a large volume of ether. The ether solution quickly deposited star-shaped crystalline aggregates of the base. It was recrystallized from ether and sublimed in a high vacuum at 130°. It has the melting point 128.5–129°, $(\alpha)^{21}D$ −79.2° (alcohol, *c*, 0.48).

Anal. Calcd. for $C_{18}H_{22}N_2O_2$: C, 72.4; H, 7.4; N, 9.4. Found: C, 72.3; H, 7.4; N, 9.8.

The dihydrochloride, purified from 95% alcohol, has the melting point 300–305° (corr., evac. tube) and $(\alpha)^{24}D$ −40.7° (water, *c*, 0.88).

Anal. Calcd. for $C_{18}H_{24}Cl_2N_2O_2 + H_2O$: Cl, 18.2; H_2O, 4.6. Found: Cl, 18.2; H_2O, 3.6.

8-Diacetylaminocodide was prepared by allowing 0.5 g. of 8-aminocodide in 5 cc. of acetic anhydride to react for eighteen hours at room temperature. Neutralization with sodium carbonate yielded 0.6 g. of crystalline base, which was purified from ethyl acetate. It crystallizes with a molecule of ethyl acetate, which could not be determined directly because of the tendency of the base to sublime; the m. p. is 218–220° (decomp.); in an evacuated tube, 165–175°, solidifying and remelting at 205°; $(\alpha)^{24}D$ −83.1° (alcohol, *c*, 1.04).

Anal. Calcd. for $C_{26}H_{34}N_2O_6$: C, 66.4; H, 7.3. Found: C, 66.5, 66.4; H, 7.0, 7.1.

(10) We are indebted to Dr. B. F. Faris, Experimental Station of E. I. du Pont de Nemours and Co., for this preparation.

Tetrahydro-8-aminocodide.—A solution of 8-aminocodide in methanol, with platinum oxide, absorbed two moles of hydrogen in fifteen minutes. The base could not be obtained crystalline from solvents, but sublimed onto a cold finger in a high vacuum at 130° in large white crystals; m. p. 138.5–140°, $(\alpha)^{24}D$ −9.7° (alcohol, *c*, 1.13). It is soluble in alkali; ferric chloride test, intense blue-green.

Anal. Calcd. for $C_{18}H_{26}N_2O_2$: C, 71.5; H, 8.7. Found: C, 71.7; H, 8.6.

The dihydrochloride was prepared with alcoholic hydrogen chloride and purified from absolute alcohol; $(\alpha)^{24}D$ +6.6° (water, *c*, 0.91).

Anal. Calcd. for $C_{18}H_{28}Cl_2N_2O_2$: Cl, 18.9. Found: Cl, 18.2.

Dihydro-8-aminocodide.—A suspension of 2.3 g. of 8-aminocodide dihydrochloride in 20 cc. of glacial acetic acid with 50 mg. of platinum oxide absorbed about 1.7 moles of hydrogen in thirty minutes. The product was precipitated with excess dilute sodium hydroxide, brought into ether, and the ethereal solution was extracted several times with dilute alkali. The dihydro compound could not be obtained crystalline, and was distilled twice in a high vacuum at 170°. It consisted of a colorless, glassy solid having $(\alpha)^{21}D$ −28.7° (alcohol, *c*, 1.08). The base is so soluble in water (like 8-aminocodide itself) that the absence of a phenolic group cannot be demonstrated with alkali. It gives a faint green ferric chloride test, and may contain a little of the tetrahydro derivative.

Anal. Calcd. for $C_{18}H_{24}N_2O_2$: C, 71.9; H, 8.0. Found: C, 71.7; H, 8.0.

The dihydrochloride, prepared with alcoholic hydrogen chloride and purified from a mixture of 1 part of absolute alcohol with 2 parts of 95% alcohol, has the m. p. 274–277° (evac. tube) and $(\alpha)^{24}D$ −14.7° (water, *c*, 1.08).

Anal. Calcd. for $C_{18}H_{26}Cl_2N_2O_2 + H_2O$: Cl, 18.1; H_2O, 4.6. Found: Cl, 17.8; H_2O, 4.6.

6-Piperidomorphide.—A mixture of 20 g. of bromomorphide and 20 g. of piperidine in a sealed evacuated tube was heated for thirty minutes in the boiling water-bath. The product was dissolved in 3 *N* hydrochloric acid, from which the base was precipitated with sodium carbonate and extracted into ether. The crystalline residue from the ether had the melting point 213–215°, yield 14.6 g. It was crystallized from ethyl acetate and sublimed four times in a high vacuum at 200°; m. p. 216–217° (evac. tube), $(\alpha)^{23}D$ −234.8° (methanol, *c*, 0.871). No other crystalline product could be isolated from the reaction.

Anal. Calcd. for $C_{22}H_{28}N_2O_2$: C, 74.9; H, 8.0; N, 7.9. Found: C, 75.2; H, 8.0; N, 8.2.

By methylation with diazomethane, 6-piperidomorphide was converted to 6-piperidocodide.

The methiodide was prepared in methanol, and separated crystalline when absolute ether was added cautiously. It crystallized as long needles from water; m. p. 236–241° (corr., evac. tube), $(\alpha)^{23}D$ −145.8° (50 vol. % alcohol, *c*, 1.05).

Anal. Calcd. for $C_{21}H_{31}IN_2O_2$: C, 53.6; H, 6.6. Found: C, 54.8, 54.3; H, 6.3, 6.2.

Dihydro-6-piperidomorphide.—A solution of 5 g. of 6-piperidomorphide in 80 cc. of ethanol with 0.2 g. of plat-

inum oxide absorbed 1 mole of hydrogen in twenty-two hours. After removal of the alcohol under diminished pressure, the oily residue was crystallized by addition of ether; yield 3.6 g., m. p. 203–210°. After four crystallizations from ethyl acetate it had the m. p. 215–217° and $(\alpha)^{24}D$ −155.9° (methanol, *c*, 0.76).

Anal. Calcd. for $C_{22}H_{30}N_2O_2$: C, 74.6; H, 8.5; N, 7.9. Found: C, 74.2; H, 8.8; N, 7.8.

6-Piperidocodide.—A mixture of 10 g. of bromocodide and 10 g. of piperidine in an evacuated sealed tube was heated in the boiling water-bath for forty-five minutes. The product was dissolved in acid, precipitated with sodium carbonate, and extracted into ether. The residue from the ether was again put through this procedure to remove piperidine. The oily product (10 g.) was treated with 6 cc. of 60% perchloric acid and diluted with 75 cc. of water, warming into solution. When the solution cooled, oily material began to separate, and was brought just into solution with alcohol. After twelve hours, the solution had deposited 6.5 g. of crystalline diperchlorate, which was purified from water to constant rotation $(\alpha)^{23}D$ −113.4° (water, *c*, 0.44); m. p. 172–175°.

Anal. Calcd. for $C_{23}H_{32}Cl_2N_2O_{10}$: Cl, 12.5. Found: Cl, 12.1.

The perchlorate was converted to the base, extracted with ether, and the residue from the ether was washed with cold 30–60° ligroin. The base was sublimed four times in a high vacuum at 130° (to constant rotation); melting point, 75–80°, $(\alpha)^{25}D$ −233.9° (methanol, *c*, 0.87).

Anal. Calcd. for $C_{23}H_{30}N_2O_2$: C, 75.4; H, 8.2; N, 7.6. Found: C, 75.1; H, 8.2; N, 7.6.

The same base and perchlorate were obtained by treatment of 6-piperidomorphide with diazomethane, likewise by heating β-chlorocodide with piperidine for six hours at 130°. Hydrogenation of 6-piperidocodide resulted in absorption of 1 mole of hydrogen, but the product was a viscous liquid from which no crystalline derivatives could be prepared. A similar substance was obtained when dihydro-6-piperidomorphide was methylated with diazomethane.

Treatment of 50 g. of bromocodide with liquid ammonia at 50° for twenty-four hours resulted in recovery of 40 g. of unchanged material. No halogen-free product could be isolated.

Summary

The reaction of α-chloromorphide and α-chlorocodide with secondary amines or ammonia proceeds with a rearrangement such that the new basic groups appear at the 8-position. The morphine derivatives that are believed to have the halogen atom in the 8-position, as bromomorphide, bromocodide, and β-chlorocodide, react with a rearrangement in the reverse sense, to give 6-aminomorphide and 6-aminocodide derivatives. The introduction of basic groups into the morphine or codeine molecule results in a considerable diminution of physiological action, especially analgesic effect.

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[CONTRIBUTION FROM THE DIVISION OF INDUSTRIAL AND CELLULOSE CHEMISTRY, MCGILL UNIVERSITY]

Studies on Lignin and Related Compounds. XLI. The Detection, Isolation and Estimation of the Syringyl Radical in Plant Products[1]

BY M. J. HUNTER AND HAROLD HIBBERT

The syringyl group was first identified in natural products as a unit in the glucoside, syringin,[2] and later in the anthocyanidin, malvin chloride.[3] Although its presence in hard wood lignin occasionally had been inferred from indirect evidence of various kinds,[4] the first isolation of syringyl components from this source was accomplished in these Laboratories.[5] More recently, it was shown that the ethanolysis of hard woods gave much higher yields[6a] than previous methods, and α-ethoxypropiovanillone and α-ethoxypropiosyringone were successfully isolated in almost equal amounts.[6b] The far-reaching implications which the corresponding hydroxy compounds (I) and (II) have for the theory of lignin structure have already been discussed exhaustively,[6,7] and it will suffice to emphasize our view that hard wood lignin is a condensation product of the unit structures (I) and (II) in equal

(1) From a thesis submitted to the Faculty of Graduate Studies and Research, McGill University, by Melvin J. Hunter in partial fulfilment of the requirements for the Degree of Doctor of Philosophy, May, 1939.

(2) Vintilesco, *J. pharm. chim.*, [6] **24**, 529 (1906).

(3) (a) Karrer, *Helv. Chim. Acta*, **10**, 67, 79 (1927); **12**, 292 (1929); **15**, 507 (1932); (b) Robinson, *J. Chem. Soc.*, 25, 1687 (1931); 1647 (1932); 206 (1933).

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