[CONTRIBUTION FROM THE COBB CHEMICAL LABORATORY, UNIVERSITY OF VIRGINIA]

The Structure of Bromomorphine[1]

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As early as 1897, Vongerichten[3] advanced the suggestion that the bromine atom in bromomorphine occupies the position at which the union of two molecules of morphine takes place when morphine is transformed by gentle oxidation into pseudomorphine. This hypothesis was based upon the observation that bromomorphine cannot be caused to undergo oxidation to a dimolecular product under the conditions imposed in the preparation of pseudomorphine, and has found general agreement among investigators in the morphine field.[4] Since the position para to the morphine phenolic hydroxyl group (C-11) and one of the ortho positions (C-4) are occupied, it has been generally believed that substitution of bromine takes place at the free ortho position, namely, C-2.[5] From a similar line of reasoning, as well as on the basis of Vongerichten's observation, the 2,2-union of two molecules of morphine in pseudomorphine has been regarded as most probable.[6]

While we do not regard Vongerichten's hypothesis as acceptable evidence for the point of linkage of the two nuclei in pseudomorphine, it must nevertheless be taken into consideration in any attack upon the pseudomorphine structural question, and the constitution of bromomorphine therefore deserves some conclusive proof. The only evidence in the literature, obtained in another connection, appears to lie in Schöpf's experiments on the closure of the 4,5-phenanthrylene oxide ring.[7] Namely, when dihydrothebainone (I) is treated with two moles of bromine, one bromine atom enters the molecule at C-5, adjacent to the carbonyl group, and a second bromine atom enters the aromatic nucleus. The second bromine may reasonably be expected to take the position para to the phenolic hydroxyl group on C-4, that is, position 1. The product obtained from closure of the 4,5-oxide ring is bromodihydrocodeinone (IV), identical with the bromodihydrocodeinone resulting from bromination of dihydrocodeinone (III), whence it may be postulated that in the latter reaction bromine was directed to the 1-position.

A fundamental assumption concerning the mode of bromination of dihydrothebainone is involved in this reasoning, however, and as is shown below in the case of desoxycodeine-C, it is by no means certain that every derivative of the morphine series necessarily undergoes bromination in the same manner as morphine.

Bromocodeine (VI), which may be prepared by methylation of bromomorphine, or by bromination of codeine, was chosen as the starting point for the structural proof. Bromocodeine methiodide, through the Hofmann degradation, was transformed to bromo-α-methylmorphimethine, and the latter, on acetolysis, yielded the bromoacetylmethylmorphol (X) already known from the work of Vongerichten.[8] Bromoacetylmethylmorphol can be hydrolyzed with methyl alcoholic

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(3) Vongerichten, *Ann.*, **297**, 210 (1897).

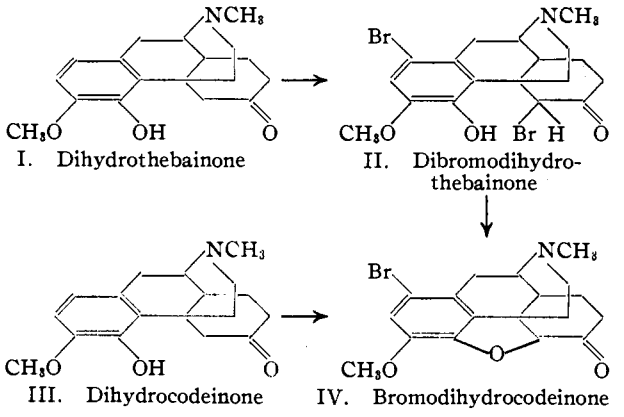
(4) Brühl, Hjelt and Aschan, "Pflanzenalkaloide," Vieweg, Braunschweig, 1900, p. 339. Morel, Leulier and Denoyel, *Bull. soc. chim.*, [4] **45**, 452 (1929).

(5) Wieland and Small, *Ann.*, **467**, 18 (1928); Small and Lutz, "Chemistry of the Opium Alkaloids," U. S. Government Printing Office, 1932, p. 146. Speyer and Rosenfeld, *Ber.*, **58**, 1110 (1925), consider the 1- or 2-positions equally probable for the halogen in bromo- and chlorocodeine. It should be noted that some evidence exists that substitution of the nitroso group in morphine [Wieland and Kappelmeier, *Ann.*, **382**, 321 (1911)] takes place at the 2-position, for through aminomorphine, a diazomorphine can be obtained that forms an anhydride of the type of the *o*-diazophenol anhydrides. The nitro group in nitrocodeine is assumed to be in the 2-position, as is the phenylazo group in phenylazomorphine. Von Braun [*Ber.*, **49**, 755 (1916)] also regards nitrocodeine as the 2-derivative. Hill (Dissertation, Frankfurt a/M, 1925) claims to have obtained a nitro derivative of (1)-bromocodeinone, a fact supporting the assumption of the 2-position for nitrocodeine derivatives. Knorr, on the other hand, considered the acetyl group in acetocodeine to occupy the 1-position [Knorr, Hörlein and Staubach, *ibid.*, **42**, 3513 (1909)]. Acetocodeine resists nitration, suggesting that the acetyl group already occupies the preferred position. Freund and Speyer [*ibid.*, **44**, 2339 (1911); *Z. angew. Chem.*, **24**, 1122 (1911)] and Speyer and Wieters [*Ber.*, **54**, 2976 (1921)] observed replacement of the acidic group in codeine-N-oxide-sulfonic acid by the nitro group, proving that codeine sulfonic acid and nitrocodeine have a similar structure. The sulfonic acids of codeine and its isomers also suffer replacement of the sulfonic acid group by bromine, but the reaction is complicated by the addition of a mole of bromine, probably at the double bond [Speyer and Krauss, *Ann.*, **432**, 243 (1923)]. The structure of these substitution products will be considered in a later communication.

(6) Wieland and Kappelmeier, *ibid.*, **382**, 310 (1911); Kappelmeier, "Konstitutionserforschung der wichtigsten Opiumalkaloide," Ahrens Sammlung, **18**, 296 (1912); Goto and Kitasato, *Ann.*, **481**, 81 (1930). The last-named investigators base their conclusion in part on analogy with β-dinaphthol, and advance no proof of structure for the pseudomorphine degradation product that they designate as bis-(2,2')-3,4-diacetylmorphol.

(7) Schöpf and Pfeiffer, *ibid.*, **483**, 157 (1930).

(8) Vongerichten, *ibid.*, **297**, 214 (1897).

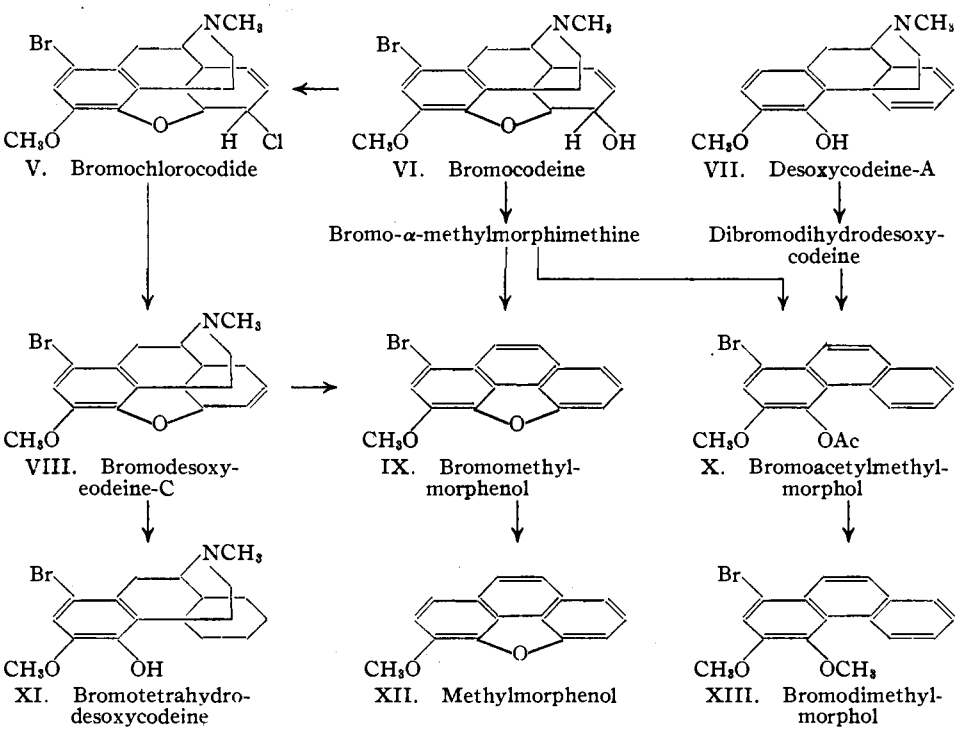


I. Dihydrothebainone
II. Dibromodihydrothebainone
III. Dihydrocodeinone
IV. Bromodihydrocodeinone

potassium hydroxide to yield bromomethylmorphol, but this product proved to be so sensitive that the successful transformation to the desired bromodimethylmorphol was accomplished only when hydrolysis and methylation proceeded simultaneously. The bromodimethylmorphol (XIII) so obtained by direct degradation of bromocodeine was identical with 1-bromo-3,4-dimethoxyphenanthrene, prepared by the Pschorr synthesis.

1-position. Whether or not pseudomorphine is 1,1′-dimorphine remains an open question, for we have been unable so far to accomplish the direct linking of two molecules of bromomorphine by elimination of bromine. The relationship of bromomorphine to pseudomorphine and other aromatic nuclear substituted morphine derivatives will be the subject of further experiments.

It is evident that, insofar as bromination is concerned, the orienting influence of the ether oxygen atom attached to the 4-position is the decisive factor, for as far as definite products can be isolated in the bromination of morphine and codeine, the bromine atom has entered in the para position to this oxygen. This predominant orienting effect of the 4-oxygen naturally is exerted by the 4-hydroxy derivatives of the codeine series, as was assumed by Schöpf in the above-mentioned bromination of dihydrothebainone. We have demonstrated this conclusively by the bromination of desoxycodeine-A (VII) and ace-



V. Bromochlorocodide
VI. Bromocodeine
VII. Desoxycodeine-A
Bromo-α-methylmorphimethine
Dibromodihydrodesoxycodeine
VIII. Bromodesoxyeodeine-C
IX. Bromomethylmorphenol
X. Bromoacetylmethylmorphol
XI. Bromotetrahydrodesoxycodeine
XII. Methylmorphenol
XIII. Bromodimethylmorphol

For further comparison, the other possibility, 2-bromo-3,4-dimethoxyphenanthrene, was synthesized by the same method, and was found to differ widely in its physical properties from the degradation product. In bromocodeine, and therefore in bromomorphine, the bromine atom occupies the

tolysis of the resulting dibromodihydrodesoxycodeine to the same bromoacetylmethylmorphol as was obtained from the acetolytic degradation of bromo-α-methylmorphimethine. The bromination of desoxycodeine-A is complicated by the fact that the molecule of hydrogen bromide formed in

substitution of the bromine atom into the aromatic nucleus adds to the system of double linkages in ring III, resulting thus in a dibromodihydrodesoxycodeine. This could be shown by treating desoxycodeine-A with hydrogen bromide in glacial acetic acid, whereby the hydrogen bromide addition product was formed, which, on treatment with bromine, then gave the dibromodihydrodesoxycodeine.

An attempt to degrade bromocodeine in another way, made at an early stage of the experimental work, led to a rather unexpected result. Knorr and Waentig[9] showed that desoxycodeine-A methyl ether methiodide yielded on alkaline degradation an unstable methyldesoxycodomethine, which decomposed spontaneously to an amine and dimethylmorphol. In the expectation that bromodesoxycodeine-A methyl ether would undergo a parallel degradation to bromodimethylmorphol, bromocodeine was converted to the known[10] bromochlorocodide (V), and this compound was subjected to zinc and alcohol reduction. As α-chlorocodide itself by this treatment is reduced to desoxycodeine-A, the analogous bromodesoxycodeine-A was expected. Apparently because of the influence of the bromine atom in the para position, however, the ether bridge was not opened, and the product obtained had the properties of a bromodesoxycodeine-C (VIII). On catalytic hydrogenation it added two moles of hydrogen in the manner characteristic of morphine derivatives containing the 6,7-double bond, giving 1 - bromotetrahydrodesoxycodeine (XI), identical with the bromotetrahydrodesoxycodeine obtained by bromination of tetrahydrodesoxycodeine.[11] In the bromination of tetrahydrodesoxycodeine is found another example of the para orienting effect of the 4-hydroxyl group, which appears to be exerted even when the hydroxyl is so weakly phenolic as to be practically indifferent. The unexpected retention of the phenanthrylene oxide ring in 1-bromodesoxycodeine-C was demonstrated beyond question by degradation. By exhaustive methylation, 1-bromodesoxycodeine-C was converted through 1-bromodesoxycodomethine-C to 1-bromomethylmorphenol (IX),[12] the same substance that we obtained in the Hofmann degradation of what we have proved to be 1-bromocodeine. 1-Bromomethylmorphenol in reaction with one mole of hydrogen (catalytic), gave methylmorphenol (XII), in which the phenanthrylene oxide ring is certainly present. The designation of the zinc–alcohol reduction product from bromochlorocodide as bromodesoxycodeine-C rests only on the characteristic behavior of the compound toward catalytic hydrogenation. For this reason, the bromination of desoxycodeine-C was undertaken. The product obtained was a tribromodihydrodesoxycodeine, $C_{18}H_{20}O_2NBr_3$, bromine having added to the alicyclic unsaturation as well as being substituted into ring I. On reduction by the catalytic method, 3 moles of hydrogen were taken up, whereby two bromine atoms were replaced by hydrogen and the ether bridge was opened reductively, probably by a mechanism similar to that which we believe operates in the catalytic reduction of α-chlorocodide. The resulting weakly phenolic base is isomeric with, but different from, bromotetrahydrodesoxycodeine, $C_{18}H_{24}O_2NBr$. On further reduction (sodium and alcohol), the last bromine atom is removed, but the halogen-free product is not tetrahydrodesoxycodeine.

The easiest synthetic approach to 1-bromo-3,4-dimethoxyphenanthrene appeared to lie in decarboxylation of 1-bromo-3,4-dimethoxyphenanthrene-10-carboxylic acid, already prepared by Pschorr[13] from condensation of 6-bromo-3,4-dimethoxyphenylacetic acid with *o*-nitrobenzaldehyde, followed by phenanthrene ring closure. A simple route to 6-bromo-3,4-dimethoxyphenylacetic acid was found in subjecting 6-bromoveratraldehyde to the Cannizzaro reaction and conversion of the resulting 6-bromoveratryl alcohol through the chloride and nitrile to the acid. Following the reaction further according to Pschorr, the bromodimethoxyphenanthrene-10-carboxylic acid was obtained, but all attempts to decarboxylate this acid resulted in simultaneous debromination. This phenomenon apparently is due to the proximity of the bromine atom and carboxyl group, so that it was necessary to turn to the corresponding 9-carboxylic acid.

To this end, vanillin was converted through acetovanillin,[14] 6-bromoacetovanillin,[15] and 2-nitro-6-bromovanillin[16] to 2-nitro-6-bromoveratr-

(9) Knorr and Waentig, *Ber.*, **40**, 3860 (1907).
(10) Vongerichten, *Ann.*, **210**, 112 (1881).
(11) Freund, *J. prakt. Chem.*, **101**, 35 (1921).
(12) (a) Vongerichten and Schrötter, *Ber.*, **15**, 1484 (1882); (b) Vongerichten, *ibid.*, **30**, 2439 (1897); (c) *ibid.*, **38**, 1851 (1905).
(13) Pschorr, *Ann.*, **391**, 37 (1912).
(14) Pschorr and Sumuleanu, *Ber.*, **32**, 3405 (1899).
(15) Raiford and Stoesser, THIS JOURNAL, **49**, 1077 (1927).
(16) Raiford and Stoesser, *ibid.*, **50**, 2556 (1928).

aldehyde.[17] This was condensed with sodium phenylacetate in acetic anhydride, yielding in addition to the desired α-phenyl-6-bromo-2-nitro-3,4-dimethoxycinnamic acid a considerable amount of 6 - bromo - 2 - nitro - 3,4 - dimethoxycinnamic acid as a by-product. By reduction of the main condensation product with ferrous sulfate, α-phenyl-6 - bromo - 2 - amino - 3,4 - dimethoxycinnamic acid was obtained, which underwent the Pschorr phenanthrene ring closure to give 1-bromo-3,4-dimethoxyphenanthrene-9-carboxylic acid.

Some difficulty was experienced in the decarboxylation. By dry distillation at 17 mm. pressure a homogeneous crystalline compound was formed which contained 2.6% less carbon than the expected bromodimethoxyphenanthrene. The analytical data indicate that this sole isolable product of the pyrolysis is the methyl ester of 1-bromo - 3,4 - dimethoxyphenanthrene - 9 - carboxylic acid, the methylation having taken place at sacrifice of the methoxyl groups in a portion of the starting material. A similar phenomenon was observed by Pschorr[18] in the dry distillation of 3,4,5-trimethoxyphenanthrene-9-carboxylic acid, where the corresponding methyl ester, together with decomposition products, was obtained. Heating in quinoline with copper powder prepared according to Gattermann[19] resulted in smooth decarboxylation, and 1-bromo-3,4-dimethoxyphenanthrene was obtained as a faintly yellow oil whose picrate and styphnate were identical with those of the bromodimethoxyphenanthrene from degradation of bromocodeine.

The synthesis of 2-bromo-3,4-dimethoxyphenanthrene proceeded from vanillin through acetovanillin, *o*-nitrovanillin, and 2-nitro-5-bromovanillin[14,16] to 5-bromo-2-nitroveratraldehyde. The Perkin reaction yielded α-phenyl-5-bromo-2-nitro-3,4-dimethoxycinnamic acid, which, through the amino acid, was converted by the Pschorr reaction to 2 - bromo - 3,4 - dimethoxyphenanthrene - 9-carboxylic acid. Attempted decarboxylation of this acid by dry distillation led to complications analogous to those mentioned in connection with the 1-bromo derivative. In this case, sufficient material was available to prove the nature of the product and to verify the hypothesis advanced above. 2-Bromo-3,4-dimethoxyphenanthrene-9-carboxylic acid was methylated with diazomethane, yielding a methyl ester identical with the compound obtained from the pyrolysis.

Decarboxylation with copper powder gave 2-bromo-3,4-dimethoxyphenanthrene, which, in contrast to the bromocodeine degradation product, is a well-crystallized compound and forms only an exceedingly unstable picrate and styphnate. We were greatly aided in this work by possessing a sample of 2-bromo-3,4-dimethoxyphenanthrene prepared by L. F. Fieser by a different method.[20]

Experimental

Degradation of Bromocodeine.—Bromocodeine was prepared by the method of Speyer and Rosenfeld[21] through treatment of codeine hydrobromide in 30% formic acid solution with hydrogen peroxide. The yields on large scale runs averaged 60% of the calculated. The bromocodeine was converted to the methiodide (96.6% yield), and the latter degraded with 10% sodium hydroxide to bromo-α-methylmorphimethine.[22] Seventy-five grams of bromocodeine methiodide gave 49 g. of pure methine base (87% yield). The yield of bromoacetylmethylmorphol from acetolytic degradation was 12 to 14% of the theoretical amount after purification by vacuum sublimation and crystallization from methanol; m. p. 165–166.5°.

Bromomethylmorphol, 1-Bromo-3-methoxy-4-hydroxyphenanthrene.—Bromoacetylmethylmorphol is exceedingly stable toward hot aqueous alkali, but is hydrolyzed readily by alcoholic alkali. One hundred milligrams of the acetyl compound in 5 cc. of 15% methanolic potassium hydroxide solution was completely soluble in ten minutes at room temperature. After five minutes more, 10 cc. of normal aqueous potassium hydroxide was added (clear solution, which oxidizes rapidly with formation of a precipitate), and an excess of 3 *N* hydrochloric acid was poured in immediately. The ether extract gave pink crystals, yield nearly quantitative. The compound crystallizes well from methanol or 30–60° ligroin in square-ended rods, which retain the pink color obstinately. It melts at 141.5–142.5° to a brown liquid.

Anal. Calcd. for $C_{15}H_{11}O_2Br$: C, 59.40; H, 3.66. Found: C, 59.82; H, 3.96.

Bromodimethylmorphol, 1-Bromo-3,4-dimethoxyphenanthrene.—Bromomethylmorphol is so sensitive in alkaline solution that its methylation could be accomplished only when carried out simultaneously with the hydrolysis of the acetyl derivative. To 15 cc. of 15% methyl alcoholic potassium hydroxide, 0.3 g. of bromoacetylmethylmorphol was added with mechanical stirring. In ten minutes solution was complete, and during the following eighty minutes 5 cc. of dimethyl sulfate was added slowly with cooling in ice. A test at this point showed methylation incomplete (characteristic crystals of bromomethylmorphol from ether). Two grams of solid potassium hydroxide and 2.5 cc. of dimethyl sulfate were added in the succeeding hour, and finally 5 cc. of aqueous 20% potassium hydroxide and 5 cc. of dimethyl sulfate were added, and

(17) Lock, *Ber.*, **68**, 1505 (1935).
(18) Pschorr, *Ann.*, **391**, 43 (1912).
(19) Naturkupfer-C was avoided in this experiment because of its greater activity and the consequent danger of debromination.
(20) Fieser and Dunn, THIS JOURNAL, **59**, 1026 (1937).
(21) Speyer and Rosenfeld, *Ber.*, **58**, 1110 (1925).
(22) Vongerichten, *Ann.*, **297**, 213 (1897).

the mixture allowed to stand in ice for twelve hours. The pasty mass was diluted with two volumes of water, the methanol removed under diminished pressure at 40°, and the solution extracted twice with an equal volume of ether. From the ether, a faintly red oil was obtained, which was treated with 250 mg. of picric acid and boiled with a little ethanol. The picrate consisted of deep red needles, 400 mg. After recrystallization from ethanol, it melted at 113–115°.

Anal. Calcd. for $C_{22}H_{16}O_9N_3Br$: N, 7.69; OCH_3, 11.35. Found: N, 7.56; OCH_3, 11.33.

A portion of the picrate was suspended in ether and shaken with small portions of normal sodium hydroxide until color no longer appeared in the aqueous layer. The ether yielded a faintly yellow oil, which was distilled onto a cold-finger in a high vacuum at 120°.

Anal. Calcd. for $C_{16}H_{13}O_2Br$: C, 60.57; H, 4.13; Br, 25.21; OCH_3, 19.55. Found: C, 60.61; H, 4.55; Br, 24.81; OCH_3, 19.57.

A droplet of the liquid 1-bromo-3,4-dimethoxyphenanthrene was boiled in ethanol with 100 mg. of styphnic acid. The brick-red styphnate, after crystallization from ethanol, melted at 105–108°.

Anal. Calcd. for $C_{22}H_{16}O_{10}N_3Br$: C, 46.97; H, 2.87; N, 7.48. Found: C, 47.26; H, 3.21; N, 7.75.

Both picrate and styphnate are somewhat unstable, and decompose after a few weeks' exposure to air. Mixed melting point determinations with the picrate and styphnate, respectively, of the synthetic 1-bromo-3,4-dimethoxyphenanthrene described below showed no depression.

1 - Bromo - 3,4 - dimethoxyphenanthrene - 10 - carboxylic Acid.—A solution of 98 g. of 6-bromoveratric aldehyde[23] in 400 cc. of saturated methyl alcoholic potassium hydroxide was heated under reflux for three hours. After dilution with 800 cc. of water, methanol was removed under diminished pressure, and the yellow oil present was extracted into ether. Acidification of the aqueous layer gave 48.2 g. of crystalline 6-bromoveratric acid of m. p. 174–178°. On distillation of the ether extract, a white pasty solid was obtained, which was recrystallized from 40 cc. of isopropyl ether; yield of 6-bromoveratryl alcohol nearly quantitative, m. p. 91–94°. Dry hydrogen chloride was passed into a solution of 59.5 g. of 6-bromoveratryl alcohol in 330 cc. of benzene for eight hours (gain in weight, 27 g.). After twelve hours, the reaction mixture was shaken with sodium carbonate solution. From the benzene, 63.7 g. of 6-bromoveratryl chloride was obtained, which crystallized in long needles from methanol, m. p. 66.5–68.5°, yield of pure product 56 g. It was analyzed by precipitation from alcohol with alcoholic silver nitrate.

Anal. Calcd. for $C_9H_{10}O_2ClBr$: Cl, 13.36. Found: Cl, 13.39.

To a hot solution of 54 g. of 6-bromoveratryl chloride in 280 cc. of alcohol, 13.8 g. of potassium cyanide and 60 cc. of water were added. The clear solution was refluxed for two hours, diluted with 400 cc. of water, and alcohol was removed under diminished pressure. The red oil which separated was extracted into ether, from which 52.8 g. of the liquid nitrile was obtained. The entire product was heated under reflux with 15 g. of potassium hydroxide in 48 cc. of alcohol for twenty-four hours, when ammonia evolution ceased. After dilution with 400 cc. of water, the red oil which separated was extracted into ether, and the aqueous layer was acidified. The precipitated oil was brought into ether, from which the crystalline 6-bromoveratrylacetic acid was obtained; yield after recrystallization from 70% alcohol, 20.4 g. (36.6%), m. p. 114–116°.

Condensation of 6-bromoveratrylacetic acid with *o*-nitrobenzaldehyde and conversion to 1-bromo-3,4-dimethoxyphenanthrene-10-carboxylic acid was carried out essentially according to Pschorr. The use of Naturkupfer-C in closing the phenanthrene ring from the diazotized α-(6-bromo-3,4-dimethoxyphenyl)-2-aminocinnamic acid always resulted in elimination of the bromine atom, but the use of copper paste prepared according to Gattermann yielded the desired 1-bromo-3,4-dimethoxyphenanthrene-10-carboxylic acid.

Dry distillation of the acid at 17 mm. pressure yielded a faintly yellow oil whose orange picrate melted at 113–115°, but depressed the melting point of bromodimethylmorphol picrate by 20°. The oil is probably the methyl ester of 1-bromo-3,4-dimethoxyphenanthrene-10-carboxylic acid. Attempted decarboxylation of the acid with copper-bronze or copper powder in quinoline gave only halogen-free products.

1-Bromo-3,4-dimethoxyphenanthrene

α - Phenyl - 6 - bromo - 2 - nitro - 3,4 - dimethoxycinnamic Acid.—Fifteen grams of 6-bromo-2-nitroveratraldehyde[17] and 8.3 g. of dry sodium phenylacetate were powdered together and heated in 90 cc. of acetic anhydride at 100° for thirty-one hours. Water (750 cc.) was added, an orange oil remaining undissolved. Concentrated ammonia was added to permanent alkalinity, and two extractions were made with 400 cc. of ether. The ether was washed with 6 *N* ammonia, which was returned to the ammoniacal portion. From the ether a small amount of the veratraldehyde derivative was recovered. The ammoniacal solution was filtered, made acid with concd. hydrochloric acid, and the precipitate was filtered out. By ether extraction a small additional portion of the crude acid was obtained, total yield 13 g., from methanol 10.7 g. of m. p. 193–200°. The combined material from several such runs was crystallized several times from methanol, α-phenyl-6-bromo-2-nitro-3,4-dimethoxycinnamic acid being the least soluble portion; yield of pure product averaged 30% of that calculated from the veratraldehyde. The melting point is 206–208°.

Anal. Calcd. for $C_{17}H_{14}O_6NBr$: Br, 19.59. Found: Br, 19.57.

6-Bromo-2-nitro-3,4-dimethoxycinnamic Acid.—The methanol mother liquors from the above separation yielded 6-bromo-2-nitro-3,4-dimethoxycinnamic acid (average 12% of the calculated amount) of m. p. 200–201° after purification from acetone and methanol.

Anal. Calcd. for $C_{11}H_{10}O_6NBr$: C, 39.76; H, 3.04; N, 4.22. Found: C, 39.73; H, 2.88; N, 3.84.

Reduction of 6-bromo-2-nitro-3,4-dimethoxycinnamic acid with ferrous sulfate in ammoniacal solution gave 6-bromo-2-amino-3,4-dimethoxycinnamic acid in 77% yield. The compound crystallizes from alcohol in matted yellow

(23) Pschorr, *Ann.*, **391**, 32 (1912).

needles of m. p. 202–203°, dissolves in dilute hydrochloric acid, from which it is precipitated and redissolved by excess of ammonia.

Anal. Calcd. for $C_{11}H_{12}O_4NBr$: C, 43.70; H, 4.00; N, 4.64; Br, 26.46. Found: C, 43.45; H, 3.64; N, 4.39; Br, 26.01.

On catalytic hydrogenation the amino acid gave a white halogen-free product of m. p. 169–170°.

α - Phenyl - 6 - bromo - 2 - amino - 3,4 - dimethoxycinnamic Acid.—Reduction of 7.5 g. of α-phenyl-6-bromo-2-nitro-3,4-dimethoxycinnamic acid with 45 g. of hydrated ferrous sulfate in ammoniacal solution according to the usual procedure gave 6.6 g. (98%) of the amino acid. It crystallizes from ethanol in yellow needles of m. p. 150–151° and dissolves in either acid or ammonia.

Anal. Calcd. for $C_{17}H_{16}O_4NBr$: Br, 21.14. Found: Br, 21.13.

It yields on catalytic reduction a halogen-free product of m. p. 120–122°.

1 - Bromo - 3,4 - dimethoxyphenanthrene - 9 - carboxylic Acid.—Two grams of α-phenyl-6-bromo-2-amino-3,4-dimethoxycinnamic acid in 20 cc. of alcohol with 5.2 cc. of 3 *N* hydrochloric acid was diazotized at 0° with a 50% solution of butyl nitrite in alcohol. After one-half hour at 0°, the orange solution was diluted with 200 cc. of water, and copper paste[24] was added in small portions under mechanical stirring. After ten hours nitrogen evolution had ceased and the light green solution had deposited a white precipitate. The solution and the copper powder were extracted with ether, in which the carboxylic acid is only sparingly soluble. The ether was extracted several times with dilute sodium carbonate, from which the acid was again precipitated with hydrochloric acid and brought into ether. The crude white crystalline product was 1.57 g. Yields in different runs averaged 72 to 82% of the calculated amount. One run made by the method of de Milt and Van Zandt[25] gave a yield of 67%. The crude product was triturated with acetone (nearly insoluble in acetone, benzene, chloroform, ethyl acetate, or methanol) and then crystallized from ethanol and from glacial acetic acid, removing a trace of color with Norit; thin colorless needles, decomposing to a black liquid with gas evolution at 260–270° (evac. tube).

Anal. Calcd. for $C_{17}H_{13}O_4Br$: Br, 22.14. Found: Br, 21.89.

1 - Bromo - 3,4 - dimethoxyphenanthrene - 9 - carboxylic Methyl Ester.—In an attempt at pyrolytic decarboxylation,[26] 1-bromo-3,4-dimethoxyphenanthrene-9-carboxylic acid was heated in 0.3-g. portions at 75 mm. pressure with a luminous flame. A dark oil, together with some unchanged acid, distilled out. The mixture was dissolved in ether and washed with sodium carbonate solution. The residue from the ether was distilled onto a cold-finger in an oil-pump vacuum at 120°, and the distillate was dissolved in ethanol, from which the product crystallized as bundles of long rods. After sublimation in a high vacuum and crystallization from acetone it melted at 123.5–125°. It does not form a picrate.

Anal. Calcd. for $C_{18}H_{15}O_4Br$: C, 57.60; H, 4.03. Found: C, 57.91: H, 4.34.

1-Bromo-3,4-dimethoxyphenanthrene.—A mixture of 0.3 g. of 1-bromo-3,4-dimethoxyphenanthrene-9-carboxylic acid, 10 cc. of quinoline, and 0.1 g. of Gattermann copper paste (washed with alcohol and ether) was heated at 240° for ten minutes. The product was diluted with 200 cc. of ether, and quinoline and unchanged carboxylic acid were removed by extraction with dilute hydrochloric acid and sodium carbonate, respectively. The residue from the ether was distilled onto a cold-finger in an oil-pump vacuum at 125°, and the oily distillate was converted to the picrate, deep red needles from alcohol, m. p. 111–113°. The mixed melting point with bromodimethylmorphol picrate was 111–113°. The styphnate crystallized in brilliant red rectangles of m. p. 106–108°, and did not depress the melting point of bromodimethylmorphol styphnate. Both picrate and styphnate decompose slowly in contact with air. The phenanthrene derivative regenerated from the picrate was a colorless liquid.

Anal. Calcd. for $C_{16}H_{13}O_2Br$: C, 60.56; H, 4.13; OCH_3, 19.57. Found: C, 60.35; H, 3.85; OCH_3, 19.02.

2-Bromo-3,4-dimethoxyphenanthrene

5-Bromo-2-nitroveratraldehyde.—Thirty grams of 5-bromo-2-nitrovanillin[16] was dissolved at 70° in 275 cc. of water containing 50 g. of sodium bicarbonate. Maintaining the temperature at 70°, 55 g. of dimethyl sulfate was added with mechanical stirring over a period of one and three-quarter hours. Forty grams of dimethyl sulfate and 40 g. of sodium bicarbonate in 200 cc. of water were added dropwise simultaneously during two hours, the mixture was cooled, and extracted with ether. The yield was 13.4 g. (42.5%) of 5-bromo-2-nitroveratraldehyde. The alkaline aqueous layer yielded on acidification 17.5 g. of starting material. The veratraldehyde derivative crystallizes from alcohol in long white needles of m. p. 70–72.5°.

Anal. Calcd. for $C_9H_8O_5NBr$: Br, 27.56; OCH_3, 21.39. Found: Br, 27.76; OCH_3, 21.96.

α-Phenyl-5-bromo-2-nitro-3,4-dimethoxycinnamic Acid.—An intimately powdered mixture of 6 g. of 5-bromo-2-nitroveratraldehyde and 3.75 g. of dry sodium phenylacetate in 36 cc. of acetic anhydride was heated for fifty minutes at 100°. The red solution was diluted with 300 cc. of water and 140 cc. of 20% sodium hydroxide, and extracted with ether. A sparingly soluble sodium salt separated (the ammonium salt behaves similarly), which was brought into solution with more water. The aqueous layer yielded on acidification 5.5 g. (65%) of crystalline product. It was purified from methanol, m. p. 231–231.5°.

Anal. Calcd. for $C_{17}H_{14}O_6NBr$: C, 50.00; H, 3.46; Br, 19.59. Found: C, 50.19; H, 3.46; Br, 19.60.

α - Phenyl - 5 - bromo - 2 - amino - 3,4 - dimethoxycinnamic Acid.—Twenty grams of the nitro acid, reduced in the usual way with 120 g. of hydrated ferrous sulfate in ammoniacal solution gave a nearly quantitative yield of the amino acid, which crystallized from alcohol in long brilliant yellow needles of melting point 175–176° (gas evolution). It is soluble in ammonia or hydrochloric acid, the hydrochloride being, however, nearly insoluble in cold water.

Anal. Calcd. for $C_{17}H_{16}O_4NBr$: C, 53.96; H, 4.27. Found: C, 53.87; H, 4.38.

(24) Gattermann, *Ber.*, **23**, 1219 (1890); Pschorr, *ibid.*, **33**, 169, note 1 (1900).

(25) De Milt and Van Zandt, THIS JOURNAL, **58**, 2044 (1936).

(26) Pschorr, *Ber.*, **29**, 500 (1896).

2 - Bromo - 3,4 - dimethoxyphenanthrene - 9 - carboxylic Acid.—Ten grams of the amino acid in 250 cc. of alcohol with 26 cc. of 3 *N* hydrochloric acid was diazotized with butyl nitrite. The diazonium compound was treated with Gattermann copper paste in small portions with mechanical stirring for six hours, and the product isolated as in the case of the 1-bromo derivative. The sodium salt causes some trouble because of its slight solubility. The yield of acid, recrystallized from acetone, was 95% of the calculated amount. It separates from acetone in faintly pink crystals melting at 237.5–238.5°.

Anal. Calcd. for $C_{17}H_{13}O_4Br$: C, 56.51; H, 3.63. Found: C, 56.65; H, 3.65.

2 - Bromo - 3,4 - dimethoxyphenanthrene - 9 - carboxylic Methyl Ester.—Attempted decarboxylation by the pyrolytic method at 75 mm. with a luminous flame resulted chiefly in formation of the methyl ester, together with decomposition products. The ester, isolated as in the 1-bromo series, crystallizes from methanol in 6-sided prisms, m. p. 114–116°. The same product was obtained when 2-bromo-3,4-dimethoxyphenanthrene-9-carboxylic acid was treated with diazomethane.

Anal. Calcd. for $C_{18}H_{15}O_4Br$: C, 57.60; H, 4.03. Found: C, 57.65; H, 4.07.

3,4-Dimethoxyphenanthrene-9-carboxylic Methyl Ester.—Ninety milligrams of the above-described methyl ester, in the presence of palladium–barium sulfate, absorbed 4 cc. of hydrogen. The product was sublimed once at 110° in an oil-pump vacuum, white crystals of m. p. 95–96°. The analytical values indicate that it may not have been quite pure.

Anal. Calcd. for $C_{18}H_{16}O_4$: C, 72.94; H, 5.44; OCH_3, 31.4; mol. wt., 296.12. Found: C, 72.26; H, 5.26; OCH_3, 29.9; mol. wt. (Rast), 287.

2-Bromo-3,4-dimethoxyphenanthrene.—A solution of 0.5 g. of 2-bromo-3,4-dimethoxyphenanthrene-9-carboxylic acid in 10 cc. of quinoline with 0.4 g. of Gattermann copper paste (washed with alcohol and ether) was heated at 245° for ten minutes. The product, isolated as in the 1-bromo series, was a red oil, which was distilled onto a cold-finger in an oil-pump vacuum at 120°. The white crystalline product was recrystallized twice from methanol, granular colorless crystals of m. p. 78.5–79.5°, mixed m. p. with 2-bromo-3,4-dimethoxyphenanthrene supplied by Fieser and Dunn, 78.2–79°. Like Fieser's sample, the picrate and styphnate form only in the presence of a large excess of picric or styphnic acid, and cannot be recrystallized.

Anal. Calcd. for $C_{16}H_{13}O_2Br$: C, 60.56; H, 4.13; Br, 25.21. Found: C, 60.34; H, 4.04; Br, 24.79.

Bromodesoxycodeine-C.—Bromochlorocodide[27] was prepared by a method parallel to that of Small and Cohen[28] for α-chlorocodide. A solution of 79 g. of bromocodeine in 125 cc. of absolute chloroform was treated at 0° under mechanical stirring with 62.5 g. of phosphorus pentachloride in 65 cc. of chloroform. The product, isolated as in the case of α-chlorocodide and crystallized from methanol, had the melting point 131–133.5°, yields 65–72% of the calculated amount. It shows in alcohol $[\alpha]^{26}D$ −288.5° (c = 0.761).

(27) Vongerichten, *Ann.*, **210**, 105 (1881).

(28) Small and Cohen, THIS JOURNAL, **53**, 2221 (1931).

Sixty grams of bromochlorocodide and 120 g. of zinc dust in 900 cc. of absolute alcohol was heated under reflux for six hours, stirring being maintained by a vigorous stream of carbon dioxide. On concentration of the red alcoholic solution, white hygroscopic crystals of a zinc chloride double salt separated. The salt was dissolved in 10% acetic acid, the solution was made strongly ammoniacal, and extracted with ether. The semicrystalline residue from the ether was dissolved in acetone and crystallization induced by cautious addition of water. The yield was from 45 to 72% of the calculated amount. The base gives a crystalline perchlorate of m. p. 208–210° (evac. tube). The base, purified several times from acetone and by sublimation in an oil-pump vacuum at 190° has the melting point 210–212.5° (evac. tube). It exhibits no phenolic properties; in alcohol, $[\alpha]^{26}D$ +65.9° (c = 0.531).

Anal. Calcd. for $C_{18}H_{20}O_2NBr$: C, 59.65; H, 5.58; Br, 22.07. Found: C, 59.58; H, 5.86; Br, 21.66.

Bromotetrahydrodesoxycodeine.—Bromodesoxycodeine-C in alcoholic solution in the presence of Adams catalyst absorbed two moles of hydrogen. The product crystallized from acetone apparently as a hydrate (m. p. 119–128°), from methanol unsolvated and melting at 156–157.5°. The mixed melting point with bromodihydrodesoxycodeine-D (m. p. 156–157°) was 126–128°, but with the known bromotetrahydrodesoxycodeine (m. p. 157–158°)[11] it showed no depression in mixed melting point. Bromotetrahydrodesoxycodeine has $[\alpha]^{26}D$ −28.2° (alcohol, c = 0.638).

Bromomethylmorphenol.—In the original belief that the bromodesoxycodeine-C was a phenolic bromodesoxycodeine-A, it was treated with dimethyl sulfate and alkali, as for the methylation of a phenol. The methomethyl sulfate of bromodesoxycodeine-C crystallized from the methylation mixture, white crystals decomposing with frothing at 197–212°.

When bromodesoxycodeine-C methomethyl sulfate was boiled with 5 *N* sodium hydroxide, the degradation to a phenanthrene derivative took place in one step. The product, isolated in the usual way and purified from methanol, had no phenolic properties, m. p. 118.5–119.5°. α-Bromomethylmorphenol, from degradation of bromomethylmorphimethine, melts at 123°.[12b,12c]

Anal. Calcd. for $C_{15}H_9O_2Br$: OCH_3, 10.34. Found: OCH_3, 10.44.

α-Bromomethylmorphenol prepared in this Laboratory by the method of Vongerichten showed the melting point 119–120°, and gave no depression in mixed melting point with the product in question. For further identification, the product was debrominated with hydrogen and palladium–calcium carbonate, giving methylmorphenol, no depression in mixed melting point with a known sample.

Bromination of Desoxycodeine-C.—A solution of 1.3 g. of desoxycodeine-C[29] in 10 cc. of 10% acetic acid was treated with 50 cc. of saturated bromine water, and after five minutes the heavy precipitate of perbromide was brought into solution with sulfur dioxide water. A white crystalline precipitate of hydrobromide formed immediately, and was filtered out and converted to the base; yield 1.2 g. After two crystallizations, the tribromodihydro-

(29) Small and Cohen, *ibid.*, **53**, 2225 (1931).

desoxycodeine had the melting point 184.5–185.5° (red liquid) and $[\alpha]^{26}D$ −156.7° (benzene, c = 0.434).

Anal. Calcd. for $C_{18}H_{20}O_2NBr_3$: C, 41.39; H, 3.86. Found: C, 41.04; H, 3.97.

A solution of 514 mg. of tribromodihydrodesoxycodeine in 10 cc. of alcohol with Adams catalyst absorbed three moles of hydrogen. The resulting hydrobromide yielded a monobromotetrahydrodesoxycodeine, sparkling crystals from acetone or ethyl acetate, m. p. 116–117.5°, $[\alpha]^{25}D$ −3.3° (alcohol, c = 0.305). It is soluble in dilute alkali, precipitated by carbon dioxide; ferric chloride test pale emerald-green. It is not the same as the bromotetrahydrodesoxycodeine obtained by bromination of tetrahydrodesoxycodeine.

Anal. Calcd. for $C_{18}H_{24}O_2NBr$: C, 59.00; H, 6.60. Found: C, 59.19; H, 6.69.

Reduction of 102 mg. of the monobromotetrahydrodesoxycodeine (m. p. 117°) in alcohol with 2 g. of sodium gave a nearly quantitative yield of crystalline base, which was sublimed twice in an oil-pump vacuum at 110°. It formed clumps of needles of m. p. 88–89°, halogen-free, structure uncertain. It is slightly soluble in alkali and is reprecipitated by carbon dioxide, ferric chloride test brown-green.

Anal. Found: C, 72.49; H, 7.90.

Bromination of Desoxycodeine-A.—To a solution of 10 g. of desoxycodeine-A in 100 cc. of glacial acetic acid, 6.5 g. of bromine in 50 cc. of glacial acetic acid was added slowly during four hours. Removal of acetic acid *in vacuo* and dilution with water gave a crystalline hydrobromide, which yielded a base of m. p. 189–189.5° (from acetone); $[\alpha]^{25}D$ +10.2° (benzene, c = 0.979). Analyses showed the presence of two bromine atoms, but otherwise did not agree with any reasonable formula.

When desoxycodeine-A is treated with hydrogen bromide in glacial acetic acid, a base is obtained which contains one bromine atom, and which on further treatment with bromine yields the above-mentioned dibromo compound. The hydrogen bromide addition product has the m. p. 149–151°, $[\alpha]^{25}D$ −3.8° (alcohol, c = 0.793) and likewise gives analytical data which cannot be interpreted.

Acetolysis of "dibromodihydrodesoxycodeine-A" was accomplished by heating under reflux 8.3 g. of the base with 1 g. of sodium acetate in 30 cc. of acetic anhydride. The product, isolated in the usual way and sublimed in an oil-pump vacuum, was 1-bromoacetylmethylmorphol, m. p. 163–165.5°.

Bromodihydrodesoxycodeine-D.—This compound was prepared for comparison with the other brominated desoxycodeines by treatment of dihydrodesoxycodeine-D in glacial acetic acid with the calculated amount of bromine. It likewise may be prepared using bromine water. After crystallization from acetone and methanol, it melts at 156–157° and has $[\alpha]^{26}D$ −37.6° (alcohol, c = 0.985).

Anal. Calcd. for $C_{18}H_{22}O_2NBr$: Br, 21.95. Found: Br, 22.14.

Summary

1. Bromomorphine has been degraded through bromocodeine and bromoacetylmethylmorphol to 1-bromo-3,4-dimethoxyphenanthrene.

2. The synthesis of 1-bromo-3,4-dimethoxyphenanthrene and of 2-bromo-3,4-dimethoxyphenanthrene by the Pschorr method is described.

3. Reduction of bromochlorocodide with zinc and alcohol leads to a bromodesoxycodeine-C, which can be degraded by the Hofmann method to 1-bromomethylmorphenol.

4. The bromination of desoxycodeine-A, of desoxycodeine-C, and of dihydrodesoxycodeine-D has been studied.

5. The significance of the results for the question of the structure of pseudomorphine is discussed.

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[CONTRIBUTION FROM THE KEDZIE CHEMICAL LABORATORY OF THE MICHIGAN STATE COLLEGE]

The Heat of Wetting of Activated Silica Gel[1]

BY D. T. EWING AND GEORGE T. BAUER

The structure of silica gel has been rather definitely shown by Fells and Firth[2] and Jones[3] to consist of capillary pores creating an enormous surface and internal volume and giving to a gel the property of sorption. As this large surface has associated with it a great amount of energy, destruction of this surface by water will give a heat effect whether it is done by water vapor or water liquid. To destroy this surface partially in steps and to measure the remaining surface energy was the purpose of this work.

In this investigation special attention was given to the preparation of the hydrated gel. Unless the proper precautions are observed irregular results are found in heat effect measurements. The percentage of hydrated water does not alone define the activity of the gel. It is equally important that the water is distributed in a manner to give a uniform surface energy. As a means of partially destroying the surface of the

(1) A portion of a Ph.D. thesis presented by Mr. George T. Bauer to the Graduate Faculty of the Michigan State College, December, 1936.

(2) Fells and Firth, *J. Phys. Chem.*, **29**, 241 (1925).

(3) Jones, *ibid.*, **29**, 327 (1925).