Derivatives of Morphine. II.[1] Demethylation of 14-hydroxycodeinone. 14-Hydroxymorphinone and 8,14-Dihydroxydihydromorphinone*

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Demethylation of 14-hydroxycodeinone (III) with aqueous HBr yields 14-hydroxymorphinone (IV) and 8,14-dihydroxydihydromorphinone (V) in varying proportions. V is formed from IV in alkaline medium during isolation, the double bond of the α,β-unsaturated ketone IV being hydrated with unusual ease by alkali. Control of conditions during this step of the isolation procedure permits reproducible preparation of either IV or V.

It has been found[1] that 14-hydroxydihydrocodeinone (I) can be demethylated normally with aqueous HBr to give 14-hydroxydihydromorphinone (II), a compound of considerable analgesic activity. The observation that the tertiary hydroxyl of I survived even the rather drastic conditions of the demethylation reaction[3] suggested a study of the analogous demethylation of 14-hydroxycodeinone (III).[4] Under the conditions used for the preparation and isolation of II, *i.e.*, brief treatment with concentrated HBr at 120°, removal of non-phenolic material by extraction with $CHCl_3$ from alkaline medium, and extraction of the phenolic reaction products with chloroform or chloroform-ethanol at *p*H 8–9, III was found to give varying proportions of two new phenolic substances, IV, $C_{17}H_{17}NO_4$, and V, $C_{17}H_{19}NO_5$, in modest yields. Of those compounds, IV was shown to be 14-hydroxymorphinone, the normal demethylation product of III, while V was identified as 8,14-dihydroxydihydromorphinone, the product of hydration of the double bond of IV. Separation of the two compounds was possible because of the great difference in their solubilities in ethanol and acetone.

14-Hydroxymorphinone, IV, was obtained in two mutually interconvertible forms: recrystallization from ethanol yielded beautiful square platelets of bright yellow color, while recrystallization from a very large volume of benzene gave perfectly colorless needles. The latter crystals darken above 200° and decompose at 255° to a voluminous black mass; the yellow platelets blacken at about 250°, but show no volume increase up to about 300°. Recrystallization from benzene converts the yellow form to the colorless one; the latter, on recrystallization from ethanol, in some cases even on mere contact with it, is changed to the yellow modification. The same change is produced by recrystallization from acetone. Both forms are little soluble in the common organic solvents; neither contains solvent of crystallization. Their infrared spectra in the solid state (KBr pellet) are different, whereby especially the location of the carbonyl stretching band is interesting: colorless form, 1685 cm.$^{-1}$, yellow form, 1660 cm.$^{-1}$.[5]

The structure of IV follows from its composition and physical and chemical properties: solubility in aqueous alkali with bright yellow color, typical of phenolic α,β-unsaturated ketones of the morphine series;[6] blue color with $FeCl_3$ in aqueous medium, no color in ethanolic medium, a behavior characteristic of morphine derivatives with intact oxygen bridge. The location of the carbonyl bands in the infrared spectra is additional evidence for the presence of an α,β-unsaturated ketone.

For final proof of structure, IV was converted to III by brief treatment with diazomethane, and to II by catalytic hydrogenation. Compound V, $C_{17}H_{19}NO_5$, forms fine colorless, silky needles, sparingly soluble in non-polar organic solvents; they decompose at about 222°. The compound is further distinguished from IV by its much greater solubility in ethanol, acetone, and hot water. The reaction with $FeCl_3$ is similar to that of IV. The solution in aqueous alkali is colorless, showing that V is not an α,β-unsaturated ketone; this is further confirmed by the location of the carbonyl band at 1730 cm.$^{-1}$ (Nujol).

Composition and properties suggested identification of V as 8,14-dihydroxydihydromorphinone. This assumption was proven by methylation with diazomethane to the methyl ether, VI. This compound was shown to be identical with authentic 8,14-dihydroxydihydrocodeinone (VI), prepared by the method of Vieböck:[7] reaction of thebaine (VII) with manganic acetate or lead tetraacetate in acetic acid to give VIII, which on brief treatment with hot dilute HCl yields VI. Furthermore, V was converted to IV by hot HCl, in analogy to the reaction VI → III.

The unpredictable appearance of V, sometimes as

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(1) Paper I: *J. Am. Chem. Soc.*, **77**, 5891 (1955).

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(3) *cf.* R. E. Lutz and L. F. Small, *J. Org. Chem.*, **4**, 220 (1939), concerning the unusual stability of this OH group.

(4) M. Freund and E. Speyer, *J. Prakt. Chem.*, (2) **94**, 135 (1916).

(5) The two modifications of IV are analogous to the colorless and yellow forms of the related α,β-unsaturated ketone metathebainone (IX), which were observed by L. F. Small and E. Meitzner, *J. Am. Chem. Soc.*, **55**, 4602 (1933).

(6) C. Schöpf and H. Hirsch, *Ann.*, **489**, 224 (1931); U. Weiss and N. Weiner, *J. Org. Chem.*, **14**, 194 (1934).

(7) F. Vieböck, *Ber.*, **67**, 197 (1934).

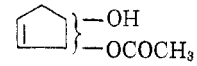
the only isolable phenolic compound from the demethylation of III, sometimes as a minor by-product, was at first tentatively ascribed to some unrecognized variation in the exposure of the alkaloidal material to *acid*, either during the demethylation itself or during subsequent operations. This assumption was based on the finding of Findlay and Small[8] that codeinone (X) undergoes slow conversion into 8-hydroxydihydrocodeinone (XI) in dilute acid; formation of V from IV would be entirely analogous to this reaction. However, experiments where the conditions of the acidic stages of the reaction were varied, failed to show any consistent influence upon the proportion of V obtained.

The explanation for the appearance of V was subsequently found in the exceptional sensitivity of IV to *alkali*. In alkaline medium, IV is converted into V with unexpected ease; the yellow color of a solution of IV in *N* NaOH fades in approximately 30 min. at room temperature, and high yields of V can be isolated from the solution. The formation of V from IV therefore takes place during the removal of the non-phenolic bases by extraction with chloroform from *alkaline* medium; consequently, strict control of the conditions during this step makes it possible to isolate at will either IV or V from the demethylation of III. Alkalinity not exceeding 0.1*N*, low temperature, and short time of exposure lead to IV together with only a small amount of V, while less mild conditions favor the preponderant or exclusive formation of V.

This ready conversion of IV into V suggested the possibility that the analogous reaction of III to give VI might likewise take place, since the reaction mixture contains much unchanged III. Small amounts of VI were actually found in the non-phenolic fractions of the demethylation experiments. The compound was isolated by treatment of the mixed non-phenolic bases with ethanol, which leaves III undissolved on account of its exceptionally low solubility in alcohol; evaporation of the filtrate to dryness, and treatment of the residue with 2*N* HCl gave the hydrochloride of VI, which is very little soluble in dilute HCl.[7] After recrystallization from 2*N* HCl and conversion to the base, pure VI was obtained, m.p. 173°. The total yield of VI obtained in this fashion was very small, indicating that the hydration of the double bond in III proceeds much less readily than that of IV.

The crude reaction mixture from the demethylation of III, after exposure to alkali, therefore contains unchanged III, the product of its demethylation (IV), of its hydration (VI), and of both reactions combined (V).

The hydroxyl groups in C_8 and C_{14} of V and VI are undoubtedly *cis* to each other. This follows not only from the strong hindrance to approach to the back side of C_8 in the morphine series, but also from the fact that Vieböck[7] obtained VIII, the intermediate in the formation of VI, on treatment of VII not only with manganic acetate, but also with lead tetraacetate in acetic acid. The latter reagent should yield a *cis*-monoacetate by analogy with the strong preponderance of *cis*- monoacyl derivatives (XII) in the reaction of cyclopentadiene with lead tetraacetate in acetic acid.[9]



XII

EXPERIMENTAL

14-Hydroxymorphinone (IV). In a round-bottom flask equipped with reflux condenser, stirrer, and thermometer, 300 ml. concentrated aqueous hydrobromic acid was heated to 90–100°; 30 g. 14-hydroxycodeinone (III) was added in one portion, the temperature of the stirred liquid was brought to 115° as fast as possible, and kept between 115 and 120° for 12 min. III dissolved rapidly, and the solution turned dark brown. The flask was next immersed in an ice bath and 600 g. ice was added, followed by dropwise addition, with continued mechanical stirring and ice-cooling, of 10% aqueous NaOH to neutral reaction. Near neutrality, a flocculent precipitate appeared, and the solution became darker. Ten per cent aqueous NaOH was next added rapidly to a final concentration of 0.1*N*, and the dark brown, ice-cold solution was extracted four times with chloroform *as fast as possible*. The extracts contained the non-phenolic bases (see below). The aqueous layer was *at once* acidified with dilute hydrochloric acid and treated with charcoal. The *p*H of the yellow filtrate was adjusted with aqueous ammonia to pink reaction on phenolphthalein paper, and the filtrate was extracted about 10 times with chloroform-ethanol (2:1).[10] The combined extracts were dried with sodium sulfate, filtered, and evaporated under reduced pressure. The solid residue was kept at room temperature for about 24 hr. with 60 ml. acetone, which dissolved the V present. The insoluble residue of IV usually weighed 10–15 g., although the yields were rather variable. Evaporation of the mother liquors and treatment of the residue with a small volume (about 10 ml.) of acetone at room temperature left another small crop of IV undissolved. The crude IV, recrystallized from about 70 volumes of boiling ethanol, yielded bright yellow square platelets, while purification from about 300 volumes of boiling benzene gave colorless needles. Recrystallization of the yellow form from benzene yields the colorless modification; the reverse change takes place on recrystallization from ethanol or acetone.

The *hydrochloride* of IV is crystalline and insoluble in ethanol and dilute HCl (1:1). IV was not precipitated by aqueous perchloric acid or Reinecke-salt, or by alcoholic picric acid; it did not give any color with *m*-dinitrobenzene and alkali.

Anal.[11] Calcd. for $C_{17}H_{17}NO_4$: C, 68.21; H, 5.73. Found: (*a*) Colorless form (dried in vacuo at 120°; no weight loss) C, 68.46; H, 5.97. (*b*) Yellow form (dried in vacuo at 78° to constant weight; no loss in weight, no change in color) C, 68.25; H, 5.68. Microhydrogenation:[11] 8.012 mg. IV (colorless form) took up 0.621 ml. hydrogen; calcd. for one molar equivalent 0.600 ml. (Pd-charcoal as catalyst).

(8) S. P. Findlay and L. F. Small, *J. Am. Chem. Soc.*, **73**, 4001 (1951).

(9) F. V. Brutcher, Jr., and F. J. Vara, *J. Am. Chem. Soc.*, **78**, 5695 (1956).

(10) A. Stoll, J. Renz, and W. Kreis, *Helv. Chim. Acta*, **20**, 1484 (1937).

(11) Microanalyses by Schwarzkopf Microanalytical Laboratory, Woodside 77, N. Y.

Methylation of 14-hydroxymorphinone. Treatment of 30 mg. IV (colorless form) in ice-cold methanol with a slight excess of ethereal diazomethane for 15 min., evaporation of the solvent, and recrystallization of the residue from methanol gave 14-hydroxycodeinone (III), m.p. and mixed m.p. 276–278° (decomp.). The infrared spectrum (KBr pellet) was identical with that of an authentic sample. A part of the material was converted to the perchlorate; m.p. and mixed m.p. with an authentic sample 246–247° (Lutz and Small[3] gave m.p. 241–242°).

Catalytic hydrogenation of 14-hydroxymorphinone. Four hundred mg. IV (yellow form), dissolved in a slight excess of dilute HCl, was reduced with Pd-charcoal as catalyst. After the end of the reaction, the catalyst was filtered off, the filtrate was evaporated *in vacuo*, and the crystalline residue of II hydrochloride was dissolved in water. Addition of a few drops of aqueous ammonia precipitated 14-hydroxydihydromorphinone (II), 250 mg., m.p. 245–247°. Extraction of the filtrate with chloroform gave an additional 64 mg. Recrystallization from ethanol and ethyl acetate gave pure II, m.p. and mixed m.p. 250° (decomp.).

8,14-Dihydroxydihydromorphinone (V). *A. By demethylation of 14-hydroxycodeinone.* The demethylation of III was carried out as described before; however, after cooling and addition of ice, the solution was made strongly alkaline by adding, dropwise and with stirring and ice-cooling, a solution of 120 g. NaOH in 200 ml. water. After removal of the nonphenolic bases from the alkaline liquid by extraction with chloroform, the aqueous layer was acidified with dilute HCl, treated with charcoal, and adjusted to a *p*H of approximately 8 with aqueous ammonia. It was next seeded with V and allowed to stand for 1–2 days at room temperature. Much of the V present crystallized out; the remainder could be obtained from the filtrate by extraction with chloroform-ethanol (2:1). The crude yield was up to about 60%.

The product was purified by dissolving it in a small amount of warm acetone, treating with charcoal, and diluting the filtrate with twice its volume of water; pure V crystallized from the solution in long silky needles. Alternatively, the compound could be purified by recrystallization from hot water. It decomposes at about 220–222° (bath preheated to 200°), the melting point depending somewhat upon the rate of heating. The compound is little soluble in benzene; the solution in aqueous NaOH is colorless.

Anal. Calcd. for $C_{17}H_{19}NO_5$: C, 64.34; H, 5.88. Found (dried *in vacuo* at 100°): C, 64.23; H, 5.87.

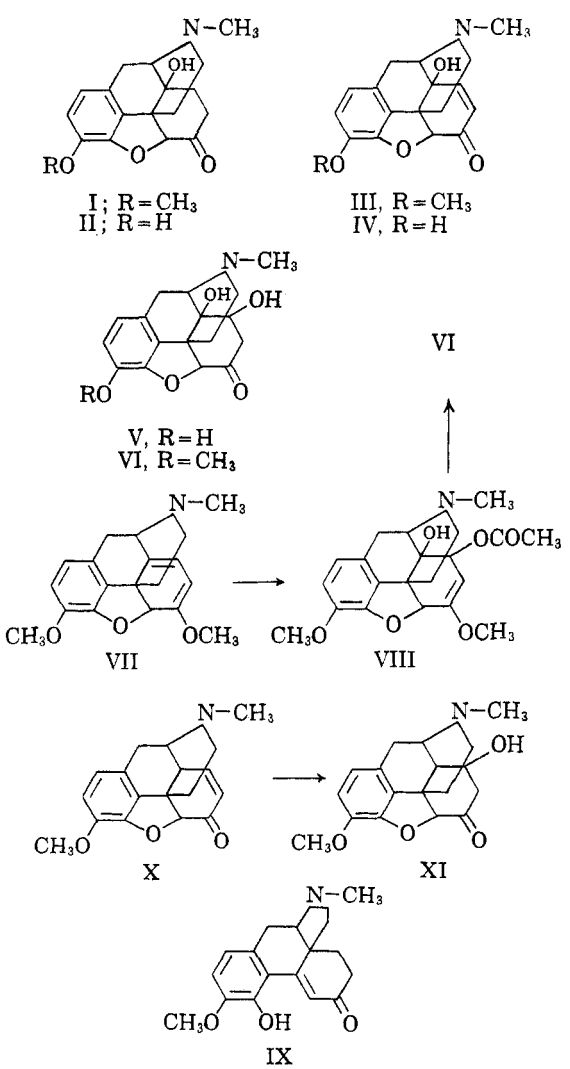
B. By hydration of 14-hydroxymorphinone. Two tenths of a gram of pure IV (yellow form) was dissolved at room temperature in 20 ml. normal NaOH, and the intensely yellow solution was kept at room temperature. The color was much less intense after 10 min., and after about 30 min. it had faded to a pale yellow which did not undergo any further change within another 30 min. The base was isolated as described before. Evaporation of the chloroform-ethanol extracts gave 0.15 g. V, which was purified from ethanol-water to give the pure compound, m.p. and mixed m.p. 222° (decomp.).

Methylation of 8,14-dihydroxydihydromorphinone. Pure V (200 mg.) was dissolved at room temperature in 10 ml. methanol. To the ice-cold solution, a slight excess of ethereal diazomethane was added. After standing at room temperature for 15 min., the solution was evaporated completely under reduced pressure. The foamy residue was treated successively with small quantities of ethanol and benzene, which were distilled off. The solid became crystalline on rubbing with ethyl acetate. Recrystallization from very dilute ethanol gave needles, m.p. about 165° (bath preheated to about 160°), the melting point depending much upon the rate of heating.[12] The compound was therefore identified as 8,14-dihydroxydihydrocodeinone (VI) by establishing identity of the infrared spectrum with that of an authentic sample prepared by the method of Vieböck,[7] rather than by mixed melting point.

Dehydration of 8,14-dihydroxydihydromorphinone to 14-hydroxymorphinone (cf.[7]). V (0.7 g.) was warmed with a mixture of 3.2 ml. concentrated HCl and 4 ml. water in a boiling water bath for 20 min. The solution was cooled and treated with excess 5% aqueous $NaHCO_3$. The orange solution, on standing in the refrigerator for several days, deposited a small amount of unchanged V. Extraction of the filtrate with chloroform gave IV, yellow crystals from ethanol, decomp. about 250°, alone and mixed with authentic IV. The yellow color of the solution in NaOH further confirmed the identification as IV.

Non-phenolic fractions; isolation of 8,14-dihydroxydihydrocodeinone. The chloroform solution containing the nonphenolic fraction from the demethylation of III was dried over Na_2SO_4, filtered, and evaporated. The residue was treated at room temperature for 24 hr. with 30 ml. ethanol. The insoluble residue (3.5 g.) consisted mostly of unchanged III, which was purified *via* the well-crystallized perchlorate. The ethanol filtrate was evaporated to dryness under reduced pressure and the residue was taken up in 2*N* HCl. The base dissolved, and on rubbing and seeding the hydrochloride of 8,14-dihydroxydihydrocodeinone (VI) crystallized out; the salt is little soluble in 2*N* HCl.[7]

It was filtered off, washed cautiously with 2*N* HCl and with acetone, and dried; yield, 0.7 g. This crude salt was



(12) This experiment was carried out before the value of the hydrochloride of VI (see right) for purification had been observed.

purified by rapid recrystallization from hot 2*N* HCl; the white, well-crystallized compound decomposes at about 260°, after partial melting around 220°, followed by resolidification. From its solution in warm water, aqueous Na_2CO_3 precipitated the base (VI), m.p. 173° (bath preheated to 160°), alone and in mixture with authentic material. Heating of a sample of the substance with dilute HCl (1:1) in a boiling water bath for 20 min. converted to III, m.p. and mixed m.p. 275° after purification via the perchlorate.

VI forms a crystalline perchlorate of low water-solubility; decomp. 257°.

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[CONTRIBUTION NO. 368 FROM THE RESEARCH LABORATORIES OF HOFFMANN-LA ROCHE, INC.]

4-Aminomethyl-4′-aminodiphenylsulfone and Related Compounds*

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4-Aminomethyl-4′-aminodiphenylsulfone and a number of its derivatives carrying substituents in the aliphatic amino group have been prepared starting with 4-methyl-4′-nitrodiphenylsulfone. Several related compounds are described.

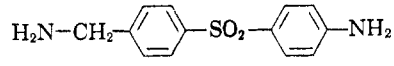
The chemotherapeutic properties of sulfanilamide are changed considerably when the aromatic amino group is replaced by the aminomethyl substituent. Whereas sulfanilamide is more active against aerobic bacteria, 4-aminomethylbenzenesulfonamide[1–4] is superior in its action against anaerobic bacteria.[2,5–8] It appeared worthwhile to prepare compounds containing an aromatic as well as an aliphatic amino group, with the hope of obtaining a sulfa drug exhibiting both types of activity. The simplest compound of this type is 4-aminomethyl-4′-aminodiphenylsulfone I. This sulfone has been described by Klarer[6] and by Dewing,[9] who prepared it from 4-acetylaminomethylbenzenesulfinic acid. In order to obtain in addition to 4-aminomethyl-4′-aminodiphenylsulfone derivatives carrying substituents in the aliphatic amino group, I carried out a different synthesis by which such derivatives are accessible in an unambiguous manner.

The key intermediate in the synthesis is 4-methyl-4′-nitrodiphenylsulfone[10] (II). The compound is prepared in high yields from *p*-thiocresol and *p*-nitrochlorobenzene over 4-methyl-4′-nitrodiphenylsulfide[11] (III), which is oxidized with hydrogen peroxide to II. The alternative procedure of condensing *p*-toluenesulfinic acid with *p*-nitrochlorobenzene gave only low yields.

The sulfone II was brominated to the bromomethyl derivative IV. The method of Genvresse,[12] using elementary bromine at 160°, gave poor yields. However, when benzoyl peroxide was added, the bromination in nitrobenzene proceeded well, resulting in yields of 70% and more of IV.

Reaction of the bromosulfone with a number of secondary amines and with benzylamine gave the amino nitro sulfones listed in Table I. Compound V, unsubstituted in the amino group, was obtained according to Mannich and Hahn[13] by the treatment of IV with hexamethylenetetramine followed by acid cleavage.

Catalytic hydrogenation of the nitro derivatives yielded the desired 4-aminomethyl-4′-aminodiphenylsulfone (I) and its alkyl derivatives, listed in Table III. The compounds lack outstanding chemo-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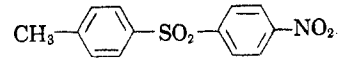
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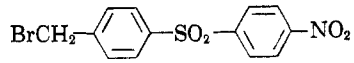
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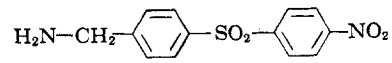
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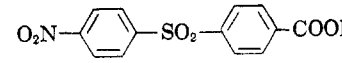
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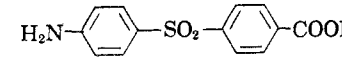
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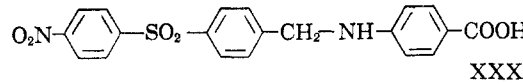
XXXVI

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* This paper is a contribution in honor of Lyndon F. Small, former Editor of the Journal.

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