of 5% palladium-on-charcoal catalyst and 3 ml. of 70% perchloric acid, and hydrogenated for 22 hr. at 2,5 atmospheres of pressure. The product consisted of 27 g. (100%) of a greenish oil which was used, without purification, for the next step. An analytical sample was obtained as colorless rosettes by several recrystallizations from ether–petroleum ether (b.p. 63–69°); m.p. 79–95°, $\bar{\nu}_{\max}^{\mathrm{CHCl_3}}$ 1712 cm.$^{-1}$.

Anal. Calcd. for $C_{20}H_{24}O_6$: C, 66.65; H, 6.71. Found: C, 67.55; H, 6.95.

The benzylamine salt of XLII was obtained, after several recrystallizations from benzene–petroleum ether (b.p. 63–69°), as colorless needles, m.p. 110–111°.

Anal. Calcd. for $C_{27}H_{33}NO_6$: C, 69.36; H, 7.11. Found: C, 69.34; H, 6.83.

(D) **2-(4′-Methoxyphenyl)-3,4-dihydro-5,6,7-trimethoxynaphthalenone (XL).**—A 27.0-g. sample of XLII was heated for 25 min. at 95° with 150 ml. of polyphosphoric acid. The product consisted of 24.5 g. (96%) of a tan solid, m.p. 112–117°, which was recrystallized from benzene–petroleum ether (b.p. 63–69°) and obtained as colorless plates, m.p. 120–121°, $\bar{\nu}_{\max}^{\mathrm{CHCl_3}}$ 1680 cm.$^{-1}$.

Anal. Calcd. for $C_{20}H_{22}O_5$: C, 70.16; H, 6.48. Found: C, 70.58; H, 6.18.

The oxime of XL was obtained, after several recrystallizations from ethanol, as stout, colorless needles, m.p. 183–185°.

Anal. Calcd. for $C_{20}H_{23}NO_5$: C, 67.21; H, 6.49. Found: C, 66.87; H, 6.29.

(E) **2-(4′-Methoxyphenyl)-3,4-dihydro-6,7,8-trimethoxynaphthalene.**—A 7.0-g. sample of XL (m.p. 120–121°) was dissolved in 50 ml. of absolute methanol and treated at 25° over a period of 3 hr. with 2.4 g. of sodium borohydride. The product consisted of 6.4 g. (96%) of a white solid, m.p. 112–114°, which yielded colorless crystals after several recrystallizations from petroleum ether (b.p. 63–69°); m.p. 115–117°, $\lambda_{\max}^{\mathrm{EtOH}}$ (ϵ) 241 mμ (14,000), 320 mμ (26,400).

Anal. Calcd. for $C_{20}H_{22}O_4$: C, 73.60; H, 6.79. Found: C, 73.28; H, 6.63.

(F) **2-(4′-Methoxyphenyl)-1,2,3,4-tetrahydro-6,7,8-trimethoxynaphthalene (XII).**—Catalytic hydrogenation of 2-(4′-methoxyphenyl)-3,4-dihydro-6,7,8-trimethoxynaphthalene yielded XII as blunt, white needles after several recrystallizations from methanol; m.p. 81–82°; $\lambda_{\max}^{\mathrm{EtOH}}$ (ϵ) 223 mμ (22,600), 277 mμ (2830), 283 mμ (2550).

Anal. Calcd. for $C_{20}H_{24}O_4$: C, 73.14; H, 7.37. Found: C, 73.46; H, 7.33.

2-(3′,4′-Dimethoxyphenyl)-1,2,3,4-tetrahydro-6,7,8-trimethoxynaphthalene (XIII). (A) **α-(3′,4′-Dimethoxyphenyl)-β-(3,4,5-trimethoxybenzoyl)-propionitrile (XXXVII).**—In the fashion indicated above, the chalcone XXVI was converted in 91% yield to a colorless powder, m.p. 143–145°, which gave colorless rosettes upon recrystallization from 95% ethanol; m.p. 144–145°.

Anal. Calcd. for $C_{21}H_{23}NO_6$: C, 65.44; H, 6.02. Found: C, 65.31; H, 5.75.

The 2,4-dinitrophenylhydrazone of XXXVII was obtained, after several recrystallizations from methanol, as brown plates, m.p. 196–197°.

Anal. Calcd. for $C_{27}H_{27}N_5O_9$: C, 57.34; H, 4.81. Found: C, 56.66; H, 4.77.

(B) **α-(3′,4′-Dimethoxyphenyl)-β-(3,4,5-trimethoxybenzoyl)-propionic Acid (XXXIX).**—Following the procedure previously indicated, the nitrile XXXVII was converted to the acid XXXIX in 53% yield, m.p. 194–196°. An analytical sample was obtained by further recrystallization from ethanol as colorless needles, m.p. 195–196°, $\bar{\nu}_{\max}^{\mathrm{CHCl_3}}$ 1680, 1710 cm.$^{-1}$.

Anal. Calcd. for $C_{21}H_{24}O_8$: C, 62.37; H, 5.98. Found: C, 62.05; H, 5.84.

(C) **2-(3′,4′-Dimethoxyphenyl)-1,2-dihydro-6,7,8-trimethoxynaphthalenone (XLI).**—A 3.3-g. sample of the keto acid XXXIX was hydrogenolyzed to 3.1 g. (100%) of the reduced acid XLIII which was not isolated but used directly in the cyclization. A 3.1-g. sample of this material was mixed with 7 ml. of polyphosphoric acid and heated on the steam-bath for 30 min. The product consisted of 1.6 g. (57%) of a neutral oil from which the ketone was obtained as feathery needles after several recrystallizations from methanol; m.p. 141–142°, $\bar{\nu}_{\max}^{\mathrm{CHCl_3}}$ 1690 cm.$^{-1}$.

Anal. Calcd. for $C_{21}H_{24}O_6$: C, 67.73; H, 6.50. Found: C, 67.29; H, 6.27.

(D) **2-(3′,4′-Dimethoxyphenyl)-1,2,3,4-tetrahydro-6,7,8-trimethoxynaphthalene (XIII).**—A 0.500-g. sample of XLI was treated with 0.5 g. of 5% palladium-on-charcoal catalyst and 0.5 ml. of 70% perchloric acid and hydrogenated for 24 hr. at 2.5 atmospheres of pressure. The crude mixture was purified by chromatography on alumina and 0.125 g. of material was obtained which, after recrystallization from methanol, yielded XIII as colorless, blunt needles, m.p. 93–94°.

Anal. Calcd. for $C_{21}H_{26}O_5$: C, 70.37; H, 7.31. Found: C, 69.51; H, 7.10.

1-Keto-1-(4′-methoxyphenyl)-3-(2′-carboxy-3,4,5-trimethoxyphenyl)-propane (Compound R).—A 10.0-g. sample of the tetralone XL was refluxed for 5 hr. with 50 ml. of acetic anhydride to give 10.4 g. of a semi-solid product containing the enol acetate (compound Q), $\bar{\nu}_{\max}^{\mathrm{CHCl_3}}$ 1680, 1775 cm.$^{-1}$. This material, without purification, was dissolved in 50 ml. of chloroform and ozonized for 1.5 hr. at 0° in a stream containing 2% ozone. The acidic product consisted of 4.1 g. (37%) of a dark-colored oil which could not be induced to crystallize.

A 2,4-dinitrophenylhydrazone of compound R was obtained, after several recrystallizations from acetone, as brilliant red, very small crystals, m.p. 226–227°.

Anal. Calcd. for $C_{26}H_{26}N_4O_{10}$: C, 56.31; H, 4.73. Found: C, 56.21; H, 4.65.

ST. LOUIS, MO.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF CALIFORNIA, BERKELEY]

The Decomposition of Quaternary Aldehydes Derived from Morphine

BY HENRY RAPOPORT, ANDREW D. BATCHO AND JOHN E. GORDON[1]

RECEIVED APRIL 24, 1958

Morphine degradation products having a formyl group at C_{13} have been found to undergo free-radical decomposition with surprising ease. The product of this decomposition is the corresponding benzofuran, the 6,7,8,9,10,14-hexahydromorphenol methyl ether, and the formyl carbon appears as carbon monoxide. This reaction, coupled with glycol cleavage of the hydroxylated 13-vinyl compound, affords a procedure for stepwise removal of carbons 15 and 16 from morphine.

During work on some colchicine degradation products, the desirability arose of having some quaternary methoxyphenylacetaldehydes for comparison purposes. Such aldehydes had been prepared from codeine and isocodeine,[2] and had been characterized as their oximes. Since an appreciable amount of the 13-vinylhexahydromorphenol (IIIb) was at hand, its conversion to the desired aldehyde

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[1] National Science Foundation Fellow, 1953–1956.

[2] H. Rapoport and G. Payne, THIS JOURNAL, **74**, 2630 (1952).

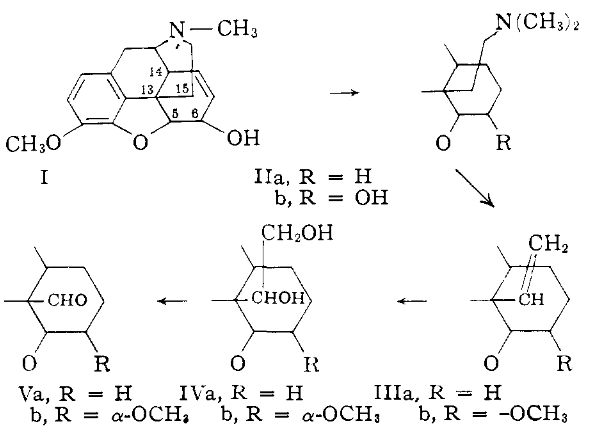
Vb was undertaken and directly and easily accomplished by hydroxylation with osmium tetroxide followed by cleavage with periodate.

The resulting aldehyde was oily, and that it was impure was obvious from its ultraviolet absorption, which should have been that of an ordinary morphine derivative containing only the veratrole chromophore ($\lambda_{max} \sim 285$ mμ, $\epsilon \sim 1500$). However, its ultraviolet spectrum was much more complex, showing a considerably higher extinction at both longer and shorter wave lengths and several additional maxima. Chromatography on alumina cleanly separated the crude product into two fractions, the first of which, about 15% of the total, was crystalline and showed no carbonyl absorption in the infrared. The remaining 85% was aldehyde and persisted as an oil after the chromatography. Although the first fraction obviously was not glycol IVb, a likely possibility was that it was an impurity carried along from the glycol cleavage reaction. Therefore, the aldehyde was converted to its crystalline oxime, this was crystallized to constant melting point, and the aldehyde was regenerated by oxime interchange with pyruvic acid.

Even after this treatment, the aldehyde Vb contained about 2% of the same impurity as shown by ultraviolet absorption. Separation on alumina actually resulted in an 18% yield of a crystalline first fraction, identical with the previous first fraction. Obviously, this material arose directly from the aldehyde itself and was not an accompanying impurity from a prior reaction. Whatever the reaction, it seemed to be occurring with great facility and since such a facile reaction with an aldehyde of this type seemed unique, we decided to investigate it in detail. The details and conclusions of the investigation are described in this report.

To assure a ready supply of starting material and remove any possible influence, steric or electronic, that the 6α-methoxyl[3] group might be exerting, most of the work was done with the corresponding desoxy compounds in which the oxygen function at C_6 is replaced by hydrogen.

The desired aldehyde (Va) was prepared from codeine (I) by tosylation followed by hydrogenolysis with lithium aluminum hydride to Δ^7-desoxycodeine. This was degraded to the methine which was isomerized to the $\Delta^{8,9}$-desoxycodeimethine before hydrogenation to tetrahydrodesoxycodeimethine (IIa) in order to minimize the formation of phenolic material. Hofmann degradation to the nitrogen-free 13-vinyl compound IIIa now took place in excellent yield since there was no hydroxyl group at C_6[4] and the over-all yield from codeine was 52%. To obtain aldehyde, the vinyl compound IIIa was converted to glycol IVa in practically quantitative yield using osmium tetroxide[5] and this was cleaved with sodium periodate.



I

IIa, R = H
b, R = OH

Va, R = H
b, R = α-OCH₃

IVa, R = H
b, R = α-OCH₃

IIIa, R = H
b, R = -OCH₃

Chromatography of the periodate reaction product gave two crystalline fractions. One was the aldehyde Va, m.p. 62–63°, and its crystallinity in this case (as compared to the oil obtained in the 6-α-methoxy series) was of considerable aid in subsequent quantitative work. The other fraction was carbonyl-free material of m.p. 48–49°, and its ultraviolet absorption was almost identical with that of the carbonyl-free compound found previously.

Again it could be shown that carbonyl-free material originated from aldehyde, since a sample of pure aldehyde, subjected to the isolation procedure, gave some of the 48–49° melting compound. Here then, with both compounds crystalline and easily separated, was the system we sought. The problem was first to establish the structure of the 48° compound and then to demonstrate how it arose from the aldehyde.

The structure of the 48° compound was delineated quite clearly by its ultraviolet absorption which is shown in Fig. 1. The maximum at 257 mμ (ϵ 13,080) indicated a styrene chromophore, and the choice for the double bond position at 5,13 rather than 13,14 was indicated strongly by the further maxima at 281 mμ (ϵ 2250) and 292 mμ (ϵ 1820). These are characteristic of the benzofuran chromophore which shows λ_{max} at 244 mμ (ϵ 11,000), 274 (2200) and 283 (2300),[6] with the expected bathochromic shift due to the 3-methoxyl group. The benzofuran formulation for the 48° compound also was consistent with the elementary analyses and the infrared spectrum in which both hydroxyl and carbonyl absorption were absent. Therefore, this material was assigned the structure 6,7,8,9,-10,14-hexahydromorphenol methyl ether (VIa).

Substantiation for this structural assignment and for the fact that no skeletal rearrangement had occurred was provided by dehydrogenation to a number of phenanthrene derivatives. Under relatively mild conditions, using palladized carbon in refluxing *p*-*t*-butyltoluene (b.p. 193°) two products were obtained; *viz.*, morphenol methyl ether (VIIa) and morphol-O^3-methyl ether (VIII), in 58 and 42% yield, respectively. A similar dehydrogenation with the corresponding 6-α-methoxy com-

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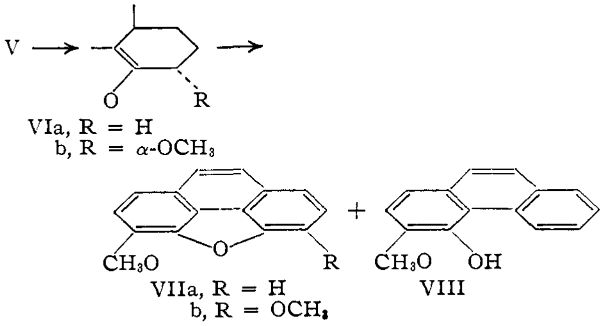
[3] The stereochemistry of the group at carbon six is designated as α when it is the same as that of the hydroxyl of codeine, *i.e.*, *trans* to the ethanamine bridge and *cis* to the oxide ring. The epimer is designated γ.

[4] Interaction with this hydroxyl group during the Hofmann degradation of IIb had led to much lower yields and a variety of products in the previous case.[2]

[5] Performic acid, which had been found to be superior to osmium tetroxide in the hydroxylation of β-Δ^6-dihydrodesoxycodeine methyl ether [M. Gates and G. Tschudi, THIS JOURNAL, **78**, 1380 (1956)] gave only a 30% yield in the present instance.

[6] R. Friedel and M. Orchin, "Ultraviolet Spectra of Aromatic Compounds," John Wiley and Sons, Inc., New York, N. Y., 1951, Figure 191.



pound VIb was a bit more complex due to the alternatives of retaining or removing the methoxyl group. The same two known compounds VIIa and VIII were obtained and, in addition, a new compound, 6-methoxymorphenol methyl ether (VIIb), was formed. Its structure was assigned on the basis of elementary and methoxyl analyses and the correspondence in ultraviolet absorption with morphenol methyl ether (VIIa) (Fig. 2).

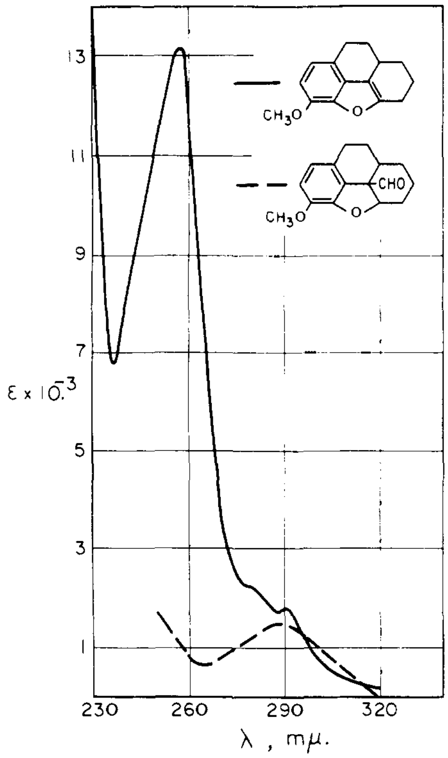


Fig. 1.—Ultraviolet absorption spectra in 95% ethanol of 6,7,8,9,10,14-hexahydromorphenol methyl ether (VIa), ———, and 13-formyl-5,6,7,8,9,10,13,14-octahydromorphenol methyl ether (Va), ---------.

That the carbonyl-free compound was the benzofuran VI was established beyond doubt by the above evidence. However, that the benzofuran had been formed from the aldehyde V under the mild conditions of the isolation procedure was surprising indeed. Decarbonylations of aldehydes have been reported a number of times, but always occurring under much more drastic conditions and resulting in different types of products (see below). Before making direct comparisons with these decarbonylations, a more detailed study was undertaken of the necessary factors in the present decomposition.

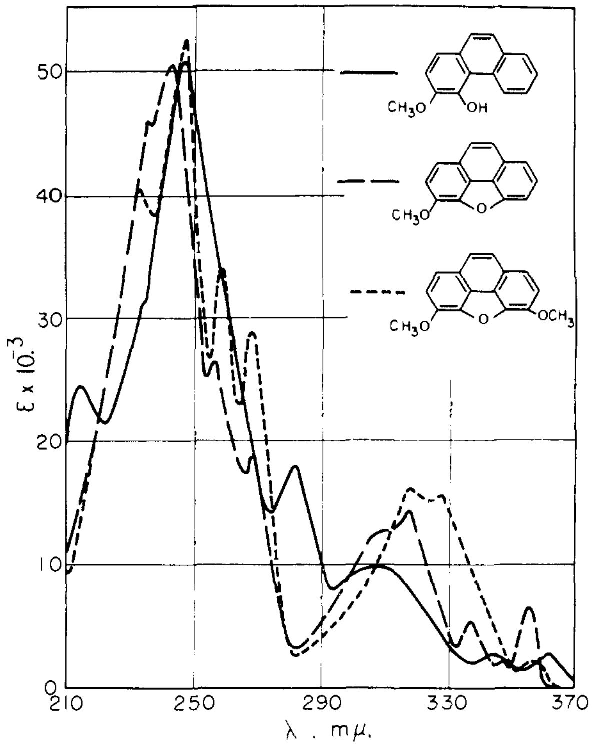


Fig. 2.—Ultraviolet absorption spectra in 95% ethanol of morphol-O^3-methyl ether (VIII), ———; morphenol methyl ether (VIIa), – – – –; and 6-methoxymorphenol methyl ether (VIIb), ---------.

The first point investigated was the stability of the aldehyde V in some solvents. In ethanol, the aldehyde V and the benzofuran VI were stable for days both in the light and dark as shown by the constancy of the optical rotations and ultraviolet spectra. This latter stability was particularly useful since it provided a reliable measure of the amount of benzofuran present through the value of the extinction coefficient at 260 mμ (Fig. 1). As was expected, addition of acid or alkali caused no change in the spectra. In chloroform and methylene chloride, at room temperature slight evidence of instability was manifest after several days, but this was far outside the range of aldehyde decomposition observed during the isolation procedure.

Possible influence of alumina on the decomposition of the aldehyde V was examined since the product had been chromatographed. With acid-washed alumina, there was no effect. With alumina (Merck) which had not been acid-washed and which gave a *p*H of 9.7 when shaken with 0.01 *M* potassium chloride (*p*H 6.0), no decomposition of aldehyde V to benzofuran VI was observed, but the alkaline column did catalyze a Cannizzaro reaction from which a 40% yield of the alcohol Xf and the acid Xg was isolated. Actually, this is a very convenient method for making both of these compounds.

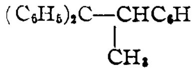
The third factor studied was the effect of heat, since the aldehyde had been exposed to slightly elevated temperatures during solvent evaporation in the isolation. Samples of aldehyde, heated at 70° (no solvent) with no precautions to exclude air, showed the presence of 23 mole % of the benzofuran after nineteen hours. At 100° in the same period of time, 37 mole % of the benzofuran was formed. That benzofuran formation was not the result of a thermal decomposition was demonstrated by conducting the reaction in an atmosphere of nitrogen, whereupon benzofuran production was greatly reduced; and when hydroquinone was added as well, benzofuran formation was completely eliminated.

The fate of the aldehydic carbon, C_{15}, was ascertained by collecting the gas above the melt of partially decomposed aldehyde and examining its infrared absorption. Clearly visible was the carbon monoxide doublet at 2150 and 2250 cm.$^{-1}$, whereas carbon dioxide absorption at 2350 cm.$^{-1}$ and absorption due to C–H stretching were totally absent. This indicated that C_{15} was converted only to carbon monoxide, a conclusion that was confirmed by individual experiments showing the absence of formaldehyde and carbon dioxide, and by a mass spectrophotometric analysis of the gaseous decomposition products.

No evidence for the presence of hydrogen in any carbon-containing fragment or for H_2 could be found. Water, if present, should be detectable in the infrared, but none was seen. As a control on the sensitivity of the method, a sample of oxalic acid was decomposed, and the carbon monoxide, carbon dioxide and water all were detected with ease. Thus we must conclude that the hydrogen on C_{15} did not terminate in the formation of water, and the fate of this hydrogen is still unanswered. Possibly it might have entered into formation of hydrogen peroxide which then was consumed in further hydroxylation of either the aldehyde V or the benzofuran VI. Some support for this hypothesis was found in the small amount of more highly oxygenated material present in each decomposition mixture.

Sufficient data were now at hand to consider a mechanism. That the reaction under observation was a free radical decomposition of the aldehyde V was indicated by (a) the requirement of oxygen and (b) the formation of carbon monoxide. However, both the ease with which it occurred and the formation of olefin as the chief if not sole product of the radical decomposition seemed at variance with what had been reported in the literature for similar reactions.

Observation of a free radical aldehyde decomposition in the liquid phase was first made by Winstein and Seubold[7] who found that β-phenylisovaleraldehyde, when heated at 130° for five hours in the presence of di-*t*-butyl peroxide, evolved 90% of the theoretical quantity of carbon monoxide. At 80°, there was little or no reaction. Additional observations of this type of reaction were made by others.[8,9] In all three cases, the products could be explained by the general mechanism in which the free radical R· then goes on to form a saturated compound by (1) abstracting a H·, (2) coupling to a dimer or (3) rearranging to a new radical which then undergoes (1) or (2). In only one instance[9] was an olefin obtained and that was presumably from the radical



$$(C_6H_5)_2C\text{—}\underset{\displaystyle CH_3}{C}HC_6H_5$$

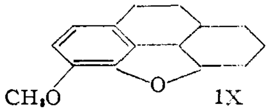
from which olefin and saturated hydrocarbon resulted in equivalent amounts. When the methyl group was replaced by hydrogen, no olefin was formed.[10]

$$RCHO \xrightarrow{-H\cdot} RCO \longrightarrow R\cdot + CO$$

In the decomposition of the aldehyde V neither the high temperatures nor the di-*t*-butyl peroxide were necessary. Oxygen at 70° was sufficient. This is probably because we have a phenylacetaldehyde and decarbonylation leads directly to the more stable tertiary benzyl radical. Instead of dimer or saturated compound Xa, we find olefin VI as the only product. If there is any analogy with the previous work,[7-9] the saturated compound Xa should have been formed in an amount at least equal to the benzofuran VI. However, Xa could be eliminated as an intermediate or product in the decomposition of the aldehyde V.

The possibility that 5,6,7,8,9,10,13,14-octahydromorphenol methyl ether (Xa) was present and escaped detection was rejected since a synthetic mixture of aldehyde, benzofuran and Xa was separated quantitatively by chromatography into its components. The further possibility that Xa was formed and very rapidly decomposed to the benzofuran was excluded by subjecting Xa to the decomposition conditions. Although some benzofuran was found, considerable Xa was recovered.[11]

Thus we are left with the explanation that the radical IX is formed which then goes on exclusively to the benzofuran VI by hydrogen atom abstraction by a chain transfer reagent such as oxygen or hydroperoxy radical. We have found this mode of decomposition also to occur with the 6-γ-methoxyaldehyde[2] as well as with aldehydes Va and Vb, and it appears to be a general reaction with this type of aldehyde.[12]



IX

A number of other 13-substituted octahydromorphenol methyl ethers were examined to see whether

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[7] S. Winstein and F. H. Seubold, Jr., This Journal, **69**, 2917 (1947).

[8] W. H. Urry and N. Nicolaides, *ibid.*, **74**, 5163 (1952).

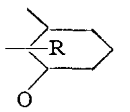
[9] D. Y. Curtin and M. J. Hurwitz, *ibid.*, **74**, 5381 (1952).

[10] In the oxidation of aldehydes, P. Thuring and A. Perret [*Helv. Chim. Acta*, **36**, 13 (1953)] have postulated similar radical intermediates which then react with oxygen to form peroxy compounds which in turn go on to oxidation products.

[11] The 5,6,7,8,9,10,13,14-octahydromorphenol methyl ether (Xa) used in these experiments was prepared by catalytic hydrogenation of the hexahydro compound VI. Assuming hydrogen addition to the less hindered side of the molecule, the stereochemistry of the hydrogenation product should be the same as that of the compound which would result upon abstraction of a H· by the radical IX.

[12] A fourth aldehyde of this type, 13-formyl-6-oxo-5,6,7,8,9,10,-13,14-octahydromorphenol methyl ether 6-ethyleneketal recently was reported by J. Kalvoda, P. Buchschacher and O. Jeger, *Helv. Chim. Acta*, **38**, 1847 (1955). Although no observation of instability was mentioned, the yields obtained could allow for the formation of some benzofuran and its elimination during the purification.

this decomposition would proceed with groups other than formyl at C_{13}. These included IIIa, IVa and the compounds X. In each case, the compound



Xa, R = H
b, R = CH_3
c, R = CH_2CH_3
d, R = CH_2OH
e, R = COOH
f, R = $\overset{H}{C}{=}NOH$
g, R = CN

was heated slightly above its m.p. open to the air for about 10 hours and then was examined in the ultraviolet. Of these nine compounds, only three (Xa, e and f) decomposed to form benzofuran. It appears likely that in each instance the intermediate is the tertiary benzyl radical IX[13] and its further reaction to introduce a double bond is strongly influenced by the lability of the hydrogen at C_5 and the stability of the benzofuran. Reaction of radical IX with aldehyde V in the type of chain propagation usually observed[7-9] undoubtedly is greatly discouraged by steric factors in both components.

This reaction is of further interest in morphine chemistry since it provides a ready method for proceeding to unrearranged degradation products in which C_{13} is tertiary rather than quaternary. With C_{13} tertiary, aromatization to substituted phenanthrenes under mild conditions is feasible. The reaction sequence from glycol IV through aldehyde V to benzofuran VI also offers a stepwise degradation scheme in which C_{16} and then C_{15} are successively excised. This may be of value in biosynthetic work with isotopes.

Experimental[14]

Tetrahydrodesoxycodeimethine (IIa).—A solution of 14.6 g. (49 mmoles) of $\Delta^{8,9}$-desoxycodeimethine (prepared as described[15] from *p*-toluenesulfonylcodeine) in 100 ml. of methanol was shaken at 16 p.s.i. hydrogen pressure in the presence of 2 g. of 5% palladium–barium sulfate catalyst. After 8 hours, an addition of 2 g. more of catalyst was made and shaking was continued for a total of 28 hours. The hydrogen consumption, which had ceased completely at this point, was 200 mole %. Filtration and concentration of the filtrate left a residue from which phenolic material was removed using diazotized sulfanilic acid.[16] The non-phenolic, oily tetrahydrodesoxycodeimethine (13.1 g., 89% yield) was converted to its crystalline **perchlorate** in 87% yield with ethanolic perchloric acid, m.p. 220–221° dec., $[\alpha]_D$ +9.5° (*c* 1.8, pyridine) (reported[16] m.p. 218–219°, $[\alpha]^{25}_D$ +4.7°).

The methiodide was prepared in methanol from tetrahydrodesoxycodeimethine liberated from its perchlorate and was crystallized from methanol; m.p. 269–270°, $[\alpha]_D$ +4° (*c* 1.0).

Anal. Calcd. for $C_{20}H_{30}O_2NI$: C, 54.2; H, 6.8; I, 28.6. Found: C, 54.4; H, 6.8; I, 28.8.

13-Vinyl-5,6,7,8,9,10,13,14-octahydromorphenol Methyl Ether (IIIa).—Tetrahydrodesoxycodeimethine methiodide (5.0 g., 11.3 mmoles) was converted to methohydroxide using the general procedure previously described,[17] and the dry methohydroxide was heated *in vacuo*. At 100°, decomposition commenced, and a pale yellow distillate was collected at 150° (0.1 mm.). This distillate was dissolved in 100 ml. of ether, the ether solution was washed in turn with 25-ml. portions of 1 *N* hydrochloric acid (three times), water, 5% sodium bicarbonate, and water, and then was evaporated to give 2.67 g., 93% yield, of a colorless oil which solidified on standing. It was crystallized from aqueous methanol and vinyl compound melting at 40–41° was obtained, $[\alpha]_D$ +60° (*c* 2.2).

Anal. Calcd. for $C_{17}H_{20}O_2$: C, 79.7; H, 7.9. Found: C, 79.8; H, 7.6.

From the aqueous acid wash, 350 mg. (10%) of tetrahydrodesoxycodeimethine was recovered after alkalization and extraction with methylene chloride.

13-(α,β-Dihydroxyethyl)-5,6,7,8,9,10,13,14-octahydromorphenol Methyl Ether (IVa).—The dark red solution obtained by mixing 1.0 g. (4 mmoles) of the vinyl compound IIIa, 10 ml. of dry benzene, 1.0 g. (4 mmoles) of osmium tetroxide and 0.7 ml. of pyridine was allowed to stand at room temperature for 36 hours. Dropwise addition with shaking of 50 ml. of hexane was followed by centrifugation, and the precipitate thus obtained was shaken for 6 hours with 50 ml. of methanol and 100 ml. of an aqueous solution containing 8.7 g. of sodium sulfite and 7.3 g. of sodium bicarbonate. The filtrate obtained on filtering through filter-aid contained two phases, and the water-methanol phase was separated and was concentrated at reduced pressure. When all the methanol had been removed, the remaining aqueous phase was extracted with three 25-ml. portions of chloroform, and the chloroform solutions were added to the benzene phase obtained after the filtration. Drying and evaporating this organic solution left 0.95 g. of the crystalline glycol which was purified further by sublimation (125° (8 μ)) and recrystallization from benzene–hexane; m.p. 128–129°, $[\alpha]_D$ −14° (*c* 1.2).

Anal. Calcd. for $C_{17}H_{22}O_4$: C, 70.3; H, 7.6. Found: C, 70.1; H, 7.4.

Cleavage of 13-(α,β-Dihydroxyethyl)-5,6,7,8,9,10,13,14-octahydromorphenol Methyl Ether (IVa).—To a warm solution of 0.37 g. (1.72 mmoles) of sodium metaperiodate in 62 ml. of water was added 12 ml. of 10% sodium bicarbonate solution followed by a solution of 0.50 g. (1.72 mmoles) of 13-(α,β-dihydroxyethyl)-5,6,7,8,9,10,13,14-octahydromorphenol methyl ether in 20 ml. of ethanol. A colorless oil separated almost immediately and the mixture was shaken at room temperature for 5 hours. The ethanol then was removed *in vacuo* and the residual aqueous suspension was extracted thoroughly with methylene chloride.

Any unreacted periodate in the aqueous phase was destroyed by addition of arsenious trioxide (0.3 g.), the solution was made acidic with hydrochloric acid and then buffered with sodium acetate, and an ethanolic solution of dimedone was added. The solution was heated on the steam-bath for 15 minutes, allowed to stand at room temperature for 3 hours, and then filtered. In this way a 60% yield of formaldehyde was isolated as the dimedone derivative, m.p. 189–190°.

The methylene chloride phase obtained above was dried and evaporated and the residue (0.41 g.), dissolved in hexane-benzene (2:1), was chromatographed on 50 g. of alumina (Merck, acid-washed). Three distinct fractions were obtained, the first of which was removed from the column with hexane–benzene (2:1). It was obtained in 20% yield and was established as **6,7,8,9,10,14-hexahydromorphenol methyl ether** (VIa), m.p. 48–49°, $[\alpha]_D$ −94° (*c* 1.8); λ_{max} 257 mμ (ϵ 13,080), 281 (2250), 292 (1820).

Anal. Calcd. for $C_{15}H_{16}O_2$: C, 78.9; H, 7.1. Found: C, 79.0; H, 7.3.

Elution with hexane–benzene (1:1) and benzene removed the second fraction, which was crystalline **13-formyl-5,6,7,8,9,10,13,14-octahydromorphenol methyl ether** (Va). It was obtained in 67% yield and melted at 62–63° (unchanged on sublimation), $[\alpha]_D$ +6° (*c* 1.0); λ_{max} 288 mμ (ϵ 1500), λ_{max} 5.83(s) μ.

Anal. Calcd. for $C_{16}H_{18}O_3$: C, 74.4; H, 7.0. Found: C, 74.4; H, 7.2.

The third fraction (57 mg.) required ethyl acetate and ethanol for elution and was obtained as a yellow oil. Its infrared spectrum showed an hydroxyl band (2.8 μ) and a carbonyl band (5.85 μ), and its analysis (C, 68.7%) indicated a substantially higher oxygen content than the previous two fractions.

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[13] The stability of the other six members of this series is evidence against an alternative mechanism in which decomposition is initiated by hydrogen atom abstraction at C_6.

[14] All melting points are corrected and those above 200° were taken in evacuated capillaries; microanalyses were performed by the Microchemical Laboratory, University of California, Berkeley. Optical rotations were measured on ethanolic solutions in one-dm. tubes at 25°, infrared spectra were taken in chloroform, and ultraviolet spectra were taken in 95% ethanol, unless otherwise specified.

[15] H. Rapoport and R. M. Bonner, THIS JOURNAL, **73**, 2872 (1951).

[16] H. Rapoport and S. Masamune, *ibid.*, **77**, 4330 (1955).

[17] H. Rapoport, *J. Org. Chem.*, **13**, 714 (1948).

Cleavage of 6-α-Methoxy-13-(α-β-dihydroxyethyl)-5,6,7,-8,9,10,13,14-octahydromorphenol Methyl Ether (IVb).—Periodate oxidation of this glycol was carried out in the same manner as described previously for glycol, and the reaction product was isolated and chromatographed similarly. The first fraction consisted of a 15% yield of **6-α-methoxy-6,7,8,9,10,14-hexahydromorphenol methyl ether** (VIb), m.p. 107–108° after crystallization from heptane and sublimation (85° (10 μ)), $[\alpha]_D$ −140° (c 1.01); λ_{max} 252 mμ (ϵ 12,400), 259 (12,950), 284 (1980), 294 (1780).

Anal. Calcd. for $C_{16}H_{18}O_3$: C, 74.4; H, 7.0; OCH_3, 24.0. Found: C, 74.4; H, 7.0; OCH_3, 23.3.

The second fraction could not be crystallized and was converted to **6-α-methoxy-13-formyl-5,6,7,8,9,10,13,14-octahydromorphenol methyl ether (Vb) oxime**, m.p. 117–119° (reported[2] m.p. 118–120°). *trans*-Oximation by heating the oxime with pyruvic acid liberated the free aldehyde which persisted as a colorless oil, λ_{max} 287 mμ (ϵ 1590).

Dehydrogenation of 6,7,8,9,10,14-Hexahydromorphenol Methyl Ether (VIa).—A solution of 6,7,8,9,10,14-hexahydromorphenol methyl ether (193 mg., 0.8 mmole) in 10 ml. of *p*-*t*-butyltoluene (b.p. 193°, boiled overnight with and distilled from 5% palladized charcoal) was heated under reflux with stirring with 100 mg. of 5% palladized charcoal. Hydrogen evolution ceased after 7.5 hours, and the mixture was filtered, the catalyst was digested with acetone (3 × 25 ml.), and the combined digests and filtrate were concentrated *in vacuo*.

The residue, dissolved in hexane, was placed on an alumina column. Elution with and crystallization from hexane gave 104 mg. of **morphenol methyl ether (VIIa)**, m.p. 63–64° (reported[18] m.p. 64–65°); ultraviolet absorption, Fig. 2.

Continued elution with hexane–benzene (5:1) removed 78 mg. of **morphol-O^3-methyl ether (VIII)**, m.p. 63–64° after crystallization from hexane (reported[18] m.p. 65°), It gave a positive test with diazotized sulfanilic acid and its ultraviolet absorption showed the expected shift on addition of alkali; for spectrum in ethanol, see Fig. 2; λ_{max} in 0.1 N ethanolic potassium hydroxide, 227 mμ (ϵ 33,400), 238 (32,500), 246 (30,400), 292 (22,800), 375 (4100).

Dehydrogenation of 6-α-Methoxy-6,7,8,9,10,14-hexahydromorphenol Methyl Ether (VIb).—The dehydrogenation was carried out exactly as described above and 170 mole % of hydrogen was evolved. The crude reaction product, after removal of all the *p*-*t*-butyltoluene, was separated into a hexane-soluble and hexane-insoluble fractions by digestion with hexane, and each was chromatographed separately on acid-washed alumina.

From the hexane-soluble fraction by elution with hexane, **morphenol methyl ether (VIIa)**, m.p. 62–63°, was obtained. Continued elution with hexane containing increasing amounts of benzene to a final composition of 10:1 removed **6-methoxymorphenol methyl ether (VIIb)**, m.p. 122–123° after crystallization from hexane; ultraviolet absorption, Fig. 2.

Anal. Calcd. for $C_{16}H_{12}O_3$: C, 76.2; H, 4.8; OCH_3, 24.6. Found: C, 76.1; H, 4.9; OCH_3, 24.6.

The hexane-insoluble fraction was digested with benzene, the digest was filtered from a small amount of insoluble material and the residue from evaporation of the benzene was chromatographed. After removal of small amounts of morphenol methyl ether and 6-methoxymorphenol methyl ether, hexane–benzene (3:1) eluted **morphol-O^3-methyl ether (VIII)**, m.p. 61–62°.

13-Hydroxymethyl-5,6,7,8,9,10,13,14-octahydromorphenol Methyl Ether (Xd).—After the addition of 5 ml. of 2.2 M lithium aluminum hydride in tetrahydrofuran to 488 mg. (1.9 mmoles) of 13-formyl-5,6,7,8,9,10,13,14-octahydromorphenol methyl ether (Va) in 10 ml. of tetrahydrofuran, the resulting solution was heated under reflux for 2.5 hours. Water then was added with cooling to decompose excess hydride, the tetrahydrofuran was removed *in vacuo*, 20 ml. of 1 N hydrochloric acid was added to the residue, and the mixture was extracted with four 15-ml. portions of methylene chloride. The combined methylene chloride extracts were dried and evaporated and the residue was chromatographed on 60 g. of alumina. Hexane–benzene removed a small amount of material and then 1% methanol in benzene eluted 428 mg. (86% yield) of 13-hydroxymethyl-5,6,7,8,9,10,13,14-octahydromorphenol methyl ether, m.p. 98–99° after sublimation at 90° (0.1 mm.), $[\alpha]_D$ +24° (c 1.0); λ_{max} 286 mμ (ϵ 1540), λ_{max} 2.95 (m)μ.

Anal. Calcd. for $C_{16}H_{20}O_3$: C, 73.8; H, 7.7. Found: C, 73.5; H, 7.6.

13-Carboxy-5,6,7,8,9,10,13,14-octahydromorphenol Methyl Ether (Xe).—When 856 mg. of the 13-formyl compound Va was applied to 107 g. of alumina (Merck, alkaline) and eluted slowly over a 3-day period, five fractions were obtained. The first fraction, eluted with hexane–benzene (2:1), was 13 mg. (1.5%) of 6,7,8,9,10,14-hexahydromorphenol methyl ether (VIa). Benzene then removed 40 mg. of an unidentified oil, followed by the third fraction, eluted with 15% ether in benzene, which was 99 mg. (12%) of recovered aldehyde. Elution was continued with 4% isopropyl alcohol in benzene and this gave 350 mg. (40%) of the 13-hydroxymethyl compound (Xd), m.p. 98–99°. The final fraction was removed with water and weighed 353 mg. (40%), m.p. 180–185°. It was recrystallized from methanol to give pure 13-carboxy-5,6,7,-8,9,10,13,14-octahydromorphenol methyl ether, m.p. 188–189°, $[\alpha]_D$ +103° (c 2.2), λ_{max} 286 mμ (ϵ 1540).

Anal. Calcd. for $C_{16}H_{20}O_4$: C, 70.1; H, 6.6. Found: C, 69.9; H, 6.7.

5,6,7,8,9,10,13,14-Octahydromorphenol Methyl Ether (Xa).—When a solution of 406 mg. (1.8 mmoles) of 6,7,8,-9,10,14-hexahydromorphenol methyl ether (VIa) in 30 ml. of 1-propanol was hydrogenated at room temperature and atmospheric pressure using 130 mg. of 5% palladized carbon as catalyst, reduction ceased after 1.5 hours and the absorption of just over 100 mole % of hydrogen. The solution was filtered, the catalyst was digested with acetone, and the combined digests and filtrate were concentrated at room temperature *in vacuo*. Sublimation of the crystalline residue at 40° (0.2 mm.) gave 5,6,7,8,9,10,13,14-octahydromorphenol methyl ether, m.p. 48–49°, $[\alpha]_D$ +68° (c 2.64), λ_{max} 288 mμ (ϵ 1220).

Anal. Calcd. for $C_{15}H_{18}O_2$: C, 78.2; H, 7.9. Found: C, 77.9; H, 8.0.

13-Methyl-5,6,7,8,9,10,13,14-octahydromorphenol Methyl Ether (Xb).—The 13-formyl compound Va was converted to its ethylene thioacetal by treating it with ethylene dithiol and boron trifluoride etherate in benzene at room temperature for 10 minutes. The crude thioacetal (m.p. 98–99°), isolated by methylene chloride extraction of the aqueous solution used to decompose the reaction mixture, was desulfurized by heating under reflux in absolute ethanol with Raney nickel. Chromatography on alumina after evaporation of the ethanol gave a crystalline fraction by elution with hexane, and this fraction was sublimed (45° (50 μ)) to yield pure 13-methyl-5,6,7,8,9,10,13,14-octahydromorphenol methyl ether, m.p. 49–50°, $[\alpha]_D$ +7° (c 0.7).

Anal. Calcd. for $C_{16}H_{20}O_2$: C, 78.7; H, 8.3. Found: C, 78.5; H, 8.2.

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[18] E. Mosettig and E. Meitzner, THIS JOURNAL, **56**, 2738 (1934).