

substrate ratio and high yield. Its success is realized only by recognizing the importance of using distilled ammonia as the solvent.⁴

Hydrolysis of **2** with aqueous methanolic oxalic acid at room temperature produces **3** in 79% yield. The infrared spectrum of **3** displays only one band in the carbonyl stretching region at 5.84μ , normal for unconjugated cyclohexanones. The n.m.r. spectrum of **3** confirms its structure by displaying singlets at τ 7.21 and 7.48 with relative intensities of 1:2, respectively.

The preparation of **4** is most easily accomplished by hydrolyzing **2** with hot 1 *N* hydrochloric acid. When the reaction is cooled, **4** precipitates and is readily isolated by filtration in 70% yield. The ease of O alkylation of **4** is illustrated by the fact that warming it in methanol in the presence of a few drops of concentrated hydrochloric acid results in an 80% yield of **5**.

The reactions of **3** and **4** are currently under study in order to determine their usefulness as intermediates in organic syntheses.

Experimental

2,7-Dimethoxy-1,4,5,8-tetrahydronaphthalene (2).—Liquid ammonia (1250 ml.) was collected in a suitable round-bottom flask, cooled to -78° , by passing the gas from a cylinder through a gas-washing tower containing solid potassium hydroxide. To the ammonia was added a solution of 2,7-dimethoxynaphthalene¹ (45.0 g., 0.24 mole) dissolved in tetrahydrofuran (200 ml.) and ethanol (150 ml.). To this stirring mixture, cooled to -78° , sodium (30.0 g., 1.3 g.-atoms) was added in small pieces over a period of 1 hr. The cooling bath was removed and the ammonia was allowed to evaporate. To the white solid mass that remained ethanol (200 ml.) was added, followed by water (2.5 l.). The crystalline product was filtered off to yield **2**, 44 g. (96%), m.p. $50\text{--}54^\circ$. Recrystallization of a small sample from methanol afforded an analytical sample, m.p. $67\text{--}68^\circ$. The infrared and n.m.r. spectra of **2** were in complete agreement with those reported.²

Anal. Calcd. for $\text{C}_{12}\text{H}_{16}\text{O}_2$: C, 74.96; H, 8.39. Found: C, 74.88; H, 8.32.

$\Delta^9,10$ -Octalin-2,7-dione (3).—To a solution of **2** (0.194 g., 0.001 mole) in methanol (10 ml.) was added 1 *M* aqueous oxalic acid (3.5 ml.) and the mixture was stirred at room temperature for 1 hr. Solid sodium bicarbonate was added to neutralize the mixture and most of the methanol was removed by evaporation at reduced pressure. Water (5 ml.) was added and the mixture was extracted with methylene chloride (three 5-ml. portions). The extracts were combined, dried over magnesium sulfate, filtered, and concentrated to a low-melting solid, 146 mg. This material was recrystallized from hexane to give **3**, 132 mg. (79%), m.p. $59.5\text{--}60.5^\circ$. The infrared spectrum of **3**

(4) An elegant investigation of the Birch reduction by Dryden⁵ has shown the necessity of using distilled ammonia for this reaction. The presence of as little as 1 p.p.m. of iron in the reaction mixture has greatly altered the course of the reaction.

(5) H. L. Dryden, Jr., G. M. Weber, R. R. Burtner, and J. A. Cella, *J. Org. Chem.*, **26**, 3237 (1961).

in CHCl_3 displayed bands at 5.84 ($\text{C}=\text{O}$) and 6.2μ ($\text{C}=\text{C}$). The n.m.r. spectrum of **3** in CCl_4 has peaks at τ 7.22 and 7.48 with relative intensities of 1:2, respectively.

Anal. Calcd. for $\text{C}_{10}\text{H}_{12}\text{O}_2$: C, 73.14; H, 7.37. Found: C, 73.12; H, 7.32.

$\Delta^9,10$ -Octalin-2,7-dione (4).—To 1 *N* hydrochloric acid (300 ml.) was added **2** (19.4 g., 0.1 mole) and the mixture was warmed to 80° with stirring for 1 hr. Upon cooling the reddish solution in ice, a precipitate resulted which was filtered off to give **4**, 11.5 g. (70%), m.p. $172\text{--}176^\circ$. Recrystallization from ethyl acetate gave a sample with m.p. $178\text{--}181^\circ$. This material showed spectral properties in ethanol and chloroform identical with those reported.²

7-Methoxy-4,4a,5,6-tetrahydro-2(3H)-naphthalenone (5).—A solution of enol **4** (0.332 g., 0.002 mole) in methanol (10 ml.) was treated with 2 drops of concentrated hydrochloric acid and warmed on the steam bath for 15 min. The mixture was neutralized with saturated sodium bicarbonate and extracted with methylene chloride (three 10-ml. portions). The combined extracts were washed with water, dried over magnesium sulfate, filtered, and concentrated under vacuum to give **5**, 0.358 g. (99%), m.p. $87\text{--}90^\circ$. Recrystallization of the sample from hexane afforded an analytical sample with m.p. $93\text{--}94^\circ$. The infrared spectrum of the sample was identical with that reported.³ The n.m.r. spectrum of **5** was as follows: singlets at τ 4.30 and 4.59 (two $\text{C}=\text{C}-\text{H}$), singlet at τ 6.31 ($\text{O}-\text{CH}_3$), and a multiplet of nine protons at τ 7.4–8.5.

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Reduction of 2,7-Dimethoxynaphthalene

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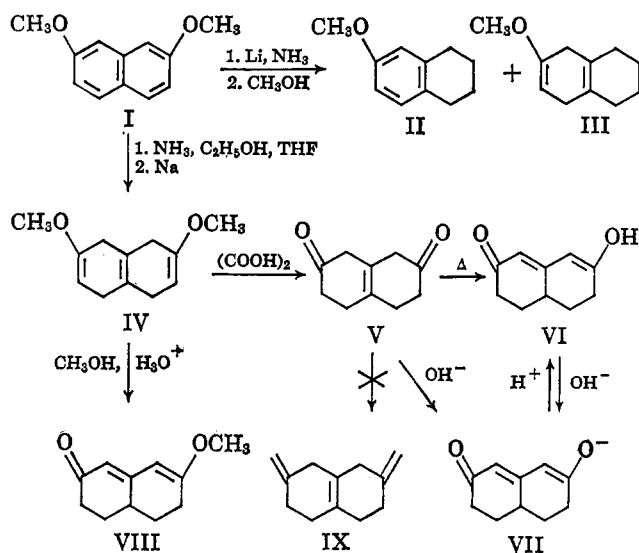
In a previous investigation of the Birch reduction of naphthalenic diethers, we reported that treatment of 2,7-dimethoxynaphthalene (I) with lithium metal in liquid ammonia in the initial absence of alcohol gave two hydrogenolysis products. These compounds were identified as 6-methoxytetralin (II) and 2-methoxy-1,4,5,6,7,8-hexahydronaphthalene (III).¹ The expected 2,7-dimethoxy-1,4,5,8-tetrahydronaphthalene (IV) was not observed in the reaction mixture. Alternatively, by following a related procedure for the reduction of 2,6-dimethoxynaphthalene,² which employed sodium metal in liquid ammonia in the presence of ethanol and the use of tetrahydrofuran as a co-solvent, we now find 2,7-dimethoxynaphthalene to be easily convertible into the desired bisenol ether (IV). This assignment of structure was confirmed by the absence of an intense maximum in the ultraviolet spectrum and by elemental analysis. The compound is apparently unstable; storage in the freezer at -20° under nitrogen retards the discoloration of the material, but after several days the sample is visibly yellow.

Mild hydrolysis by oxalic acid³ in aqueous methanol at room temperature cleaved the diether IV and formed the even less stable $\Delta^9,10$ -octalin-2,7-dione (V). The infrared spectrum of the unconjugated ketone exhibited

(1) B. Weinstein and A. H. Fenselaw, *J. Org. Chem.*, **29**, 2102 (1964).

(2) M. Kocór and W. Kotlarek, *Bull. Acad. Polon. Sci., Ser. Sci. Chim.*, **9**, 507 (1961).

(3) D. Burn and V. Petrow, *J. Chem. Soc.*, 364 (1962).



an extremely intense and broad carbonyl absorption at 1700 cm^{-1} with a lesser maximum at 1605 cm^{-1} . The ultraviolet spectrum in ethanol contained a weak absorption at $318\text{ m}\mu$, probably due to the presence of a very small amount of the conjugated isomer VI. Heating the dione V at temperatures above 60° produced the conjugated dienone VI as a sublimable, crystalline yellow compound. The visual color and the infrared spectrum served to confirm the existence of VI in the solid state as the enol form.

The ultraviolet spectrum of VI was obtained in several solvents and displayed a red shift with increasing solvent polarity, which is characteristic of $\pi \rightarrow \pi^*$ transitions (Table I). With ethanol a maximum was seen at $323\text{ m}\mu$, in agreement with a similar maximum at $322\text{ m}\mu$ exhibited by Δ^4 -3,7-diketo steroids.⁴

TABLE I

ULTRAVIOLET SPECTRA OF 2,7-DIMETHOXYNAPHTHALENE AND RELATED COMPOUNDS

Compd.	Solvent	λ_{max} , $\text{m}\mu$ (log ϵ)
I	$\text{C}_2\text{H}_5\text{OH}$	235 (4.99)
II	$\text{C}_2\text{H}_5\text{OH}$	280 (3.31)
		288 (2.25)
III	$\text{C}_2\text{H}_5\text{OH}$	None
IV	$\text{C}_2\text{H}_5\text{OH}$	278 (1.64)
V	$\text{C}_2\text{H}_5\text{OH}$	318 (2.39) ^a
	$\text{C}_2\text{H}_5\text{OH}, \text{OH}^-$	386 (4.80) ^b
		371 (4.53) ^c
VI	H_2O	328 (4.19)
		376 (3.60) ^e
	$\text{H}_2\text{O}, \text{H}^+$	328 (4.22) ^d
	$\text{H}_2\text{O}, \text{OH}^-$	380 (5.11) ^b
	$\text{C}_2\text{H}_5\text{OH}$	323 (4.39)
		385 (4.12)
	$\text{C}_2\text{H}_5\text{OH}, \text{H}^+$	323 (4.44) ^d
	$\text{C}_2\text{H}_5\text{OH}, \text{OH}^-$	385 (4.98) ^b
	$\text{C}_2\text{H}_5\text{OH}$	321 (4.41) ^e
		386 (3.72) ^e
	$\text{C}_2\text{H}_5\text{OH}, \text{H}^+$	321 (4.42) ^e
	$\text{C}_2\text{H}_5\text{OH}, \text{OH}^-$	386 (4.97) ^e
VIII	$\text{C}_2\text{H}_5\text{OH}$	312 (4.50)

^a Apparently contains about 1% of the conjugated ketone VI. ^b Addition of 1 drop of 2 *N* sodium hydroxide solution. ^c Shoulder. ^d Addition of 2 drops of 2 *N* hydrochloric acid solution. ^e Absolute ethanol.

(4) L. Dorfman, *Chem. Rev.*, **53**, 80 (1953).

Both compounds V and VI revealed an intense absorption at $386\text{ m}\mu$ in basic 95% ethanol, which could be erased by adding acid dropwise so as to cause a reversion to the conjugated dienone chromophore VI. The spectral behavior is consistent with the formation in solution of the enolate anion (VII). This information is summarized in Table I.

Treatment of compound IV with dilute mineral acid in methanol gave a keto ether (VIII), which possessed an ultraviolet maximum at $312\text{ m}\mu$. Microanalytical and n.m.r. data support structure VIII for this product. A 2,4-dinitrophenylhydrazone derivative could be prepared also. Immediate precipitation of a salt resulted when the dione V was allowed to react with the ylide from triphenylphosphonium bromide. This ylide was prepared by two different methods using *n*-butyl⁵ and dimethylsulfinyl⁶ anions. In both cases no detectable amounts of the desired 2,7-dimethylene-1,2,3,4,5,6,7,8-octahydronaphthalene (IX) or related olefins were revealed by gas chromatographic analysis of the solutions. A similar result was obtained with methylmagnesium bromide. Under these reaction conditions sufficient base is presumed to have been present so as to form the anion of VII and ultimately the corresponding insoluble salt.

Shortly after the preparation of this manuscript our attention was drawn to a report which not only verified our earlier work, but which tabulated almost the same reaction sequences as now described by us.⁷ Of immediate interest is the fact that the reported physical constants and assignment of structures for compounds IV, VI, and VIII are in agreement and that a similar conclusion is reached on the existence of anion VII. It may be noted that the *solid* material prepared by these workers and described as "1(9)-octal-2,7-dione" is actually the enol VI. Additionally, compound V was not isolated, in contrast to our observations here.

Experimental⁸

2,7-Dimethoxy-1,4,5,8-tetrahydronaphthalene (IV).—A solution of 5.00 g. (0.0266 mole) of 2,7-dimethoxynaphthalene (I)¹ in 100 ml. of anhydrous tetrahydrofuran and 150 ml. of absolute ethanol was added with stirring to 400 ml. of anhydrous liquid ammonia held at -70° . In a period of 30 min. about 20 g. (0.869 g.-atom) of freshly cut sodium wire was added to the reaction mixture. A bluish cast to the solution developed which disappeared as the sodium was consumed. The bath temperature surrounding the reaction flask hovered at -35° during this interval. The solution was stirred for a further 30 min., the flask was withdrawn from the bath, and the ammonia was allowed to evaporate overnight.

The addition of 250 ml. of water to the gray tetrahydrofuran solution produced a pale yellow oil. The aqueous phase was extracted with chloroform (three times, 500 ml.), and the combined organic extracts were washed with water (three times, 600

(5) G. Wittig and V. Schöllkopf, *Org. Syn.*, **40**, 60 (1960).(6) E. J. Corey and M. Chaykovsky, *J. Org. Chem.*, **28**, 254 (1963).(7) J. A. Marshall and N. H. Anderson, *ibid.*, **30**, 1292 (1965).

(8) Melting points and boiling points are uncorrected. Microanalyses were performed by Messrs. E. H. Meier and J. Consul of the Microanalytical Laboratory, Department of Chemistry, Stanford University. The infrared spectra were obtained on a Perkin-Elmer Model 421 double-grating instrument in potassium bromide disks and the ultraviolet spectra were taken on a Cary Model 14 spectrophotometer in grain alcohol solution, unless otherwise stated. N.m.r. spectra were determined on a Varian A-60 spectrometer in deuteriochloroform solution with tetramethylsilane as an internal standard.

ml.) and with saturated ammonium sulfate solution (once, 100 ml.). Evaporation of the chloroform solution gave 5 g. of a very pale yellow oil which solidified on standing at room temperature. The residue was sublimed directly at 50° and 0.2 mm. to provide 4.35 g. (85%) of white crystals, m.p. 62.5–63.5°. Thin layer chromatography on silica gel (ether–hexane, 1:1) indicated the sample was homogeneous, R_f 0.70. The analytical sample was obtained by two additional sublimations: m.p. 65.5–66.0°; ν_{\max} 3040, 3070 (w), 2940, 2870, 2820, 2790 (s), 1703 (mw), 1660 (s), a cluster of maxima between 1460 and 1355 (m), 1220 (s), 1140 (s), 1100, 1040, 1000 (ms), and 780 (s) cm^{-1} .

Anal. Calcd. for $\text{C}_{12}\text{H}_{16}\text{O}_2$: C, 74.97; H, 8.39. Found: C, 74.80; H, 8.31.

1,2,3,4,5,6,7,8-Octahydronaphthalene-2,7-dione (V).—Under a nitrogen atmosphere 0.292 g. (0.00152 mole) of 2,7-dimethoxytetrahydronaphthalene (IV) was added to a previously deoxygenated solution of 0.250 g. (0.00200 mole) of oxalic acid dihydrate in 1.5 ml. of water and 20.0 ml. of methanol. The mixture was warmed gently on the steam bath until the solid had dissolved. The solution was allowed to stand for 15 min. at room temperature, then 0.210 g. (0.00200 mole) of sodium carbonate was added, and the solvent was removed with a rotary evaporator. The crude product was dissolved in 25 ml. of chloroform, the organic phase was dried with anhydrous magnesium sulfate, and on evaporation there was produced 0.278 g. of a yellow oil which solidified on standing. The material was sublimed directly at 58° and 0.2 mm. to give pale yellow crystals. The analytical sample was obtained by two additional sublimations: m.p. 62.5–63.5°; R_f 0.30 (same solvent system); ν_{\max} 2700, 1700 (broad), 1605, several maxima between 1450 and 1300, 1200, 1185, 1140, 1000, and 850 cm^{-1} ; δ 2.80 (singlet, 4H, protons which are both allylic and on a carbon atom α to a carbonyl group) and 2.55 (singlet, 8H, protons which are either allylic or on a carbon atom α to a carbonyl group).

Anal. Calcd. for $\text{C}_{10}\text{H}_{12}\text{O}_2$: C, 73.14; H, 7.37. Found: C, 73.22; H, 7.57.

7-Hydroxy-1,2,3,7,8,9-hexahydronaphthalen-2-one (VI).—During the purification of 1,2,3,4,5,6,7,8-octahydronaphthalene-2,7-dione (V), a significant portion of a dark yellow substance remained unaffected at 58°. This material was induced to sublime at 135° and 0.2 mm. and afforded a yellow solid, m.p. 179.0–179.5°. The analytical sample was crystallized from water: m.p. 179.0–179.5°; R_f 0.12 (same solvent system); ν_{\max} 3400–2500 (very broad), 2950, 1595 (vs), 1530 (vs), 1345, 1335, and 1165 (ms) cm^{-1} .

Anal. Calcd. for $\text{C}_{10}\text{H}_{12}\text{O}_2$: C, 73.14; H, 7.37; neut. equiv., 164. Found: C, 72.94; H, 7.34; neut. equiv., 164.

7-Methoxy-1,2,3,7,8,9-hexahydronaphthalen-2-one (VIII).—A solution of 0.500 g. (0.00260 mole) of 2,7-dimethoxytetrahydronaphthalene (IV) in 0.1 ml. of concentrated hydrochloric acid, 2.0 ml. of water, and 35.0 ml. of methanol was allowed to stand for 2 hr. at room temperature. The solvent was removed with a rotary evaporator and the residue was sublimed at 65° and 1 mm. to yield 0.418 g. (89%) of white crystals, m.p. 86.5–87.5°. The analytical sample was obtained by two additional sublimations: m.p. 92.0–92.2°; ν_{\max} 3010 (w), 2930 (s), 1650 (s), 1605 (s), 1575 (s), and 875 (s) cm^{-1} ; δ 5.72, 5.43 (1H each, two nonequivalent vinyl protons), 3.70 (3H, vinyl methoxy), and 2.60–1.4 (9H, remaining allylic protons or protons on carbon atom α to the carbonyl group).

Anal. Calcd. for $\text{C}_{11}\text{H}_{14}\text{O}_2$: C, 74.13; H, 7.92. Found: C, 73.96; H, 7.94.

A reddish brown derivative formed when 2,4-dinitrophenylhydrazine solution was added to a methanolic solution of 2,7-dimethoxytetrahydronaphthalene (IV). After chromatographing through alumina (neutral, activity I) the dinitrophenylhydrazone was crystallized from ethyl acetate–ethanol (1:1) as short, red needles, m.p. 215.0–215.5°, $\lambda_{\max}^{\text{CHCl}_3}$ 422.5 μm ($\log \epsilon$ 4.65) and 317 μm ($\log \epsilon$ 4.33).

Anal. Calcd. for $\text{C}_{17}\text{H}_{18}\text{N}_4\text{O}_8$: C, 56.98; H, 5.06; N, 15.63. Found: C, 56.49; H, 5.18; N, 15.80.

Reactions Attempted with 1,2,3,4,5,6,7,8-Octahydronaphthalene-2,7-dione (V).—Freshly prepared dione IV was added in turn to triphenylmethylphosphonium bromide and methylmagnesium bromide solutions. In each case a yellow precipitate formed as soon as the two phases were mixed together. Aliquots of each solution were analyzed for the presence of volatile products by gas chromatography. With reaction times varying from 2 to 4 hr., no evidence was seen for the formation of compound IX or related olefins.

Synthesis of Phospho Diester Using Phosphoryl Chloride

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It has been known that the phosphorylation of 2',3'-O-isopropylidene nucleoside with phosphoryl chloride affords phosphorylated products in addition to expected nucleoside monophosphate. Levene and Tipson¹ have reported the formation of adenosine N⁶,5'-diphosphate in addition to the 5'-monophosphate by the reaction of 2',3'-O-isopropylideneadenosine with phosphoryl chloride, but not the formation of any other phosphorylated products in the case of 2',3'-O-isopropylideneinosine.² Recently Khorana,³ *et al.*, attempted to apply this method to 2',3'-O-isopropylidene-guanosine and obtained a mixture which consists of guanosine 5'-monophosphate and a small amount of phosphorus-containing products, such as guanosine 5'-diphosphate, 5'-triphosphate, and higher phosphates.

In the present work phosphorylation of 2',3'-O-isopropylideneinosine (I) with 1.4 equiv. of phosphoryl chloride in anhydrous pyridine and hydrolytic removal of the isopropylidene group gave a mixture of two products. Crystallization of the sodium salt of the mixture afforded a precipitate of the major component which was identified as inosine 5'-monophosphate (II). The minor component was obtained in pure state from the mother liquors by fractional crystallization of the barium salt. It showed the ultraviolet absorption spectrum characteristic of hypoxanthine and accounted for 20% of the ultraviolet-absorbing material in the crude product. Potentiometric titration with acid suggested the product was diinosine 5'-phosphate (III), since no basic group corresponding to a phosphate dianion was observed. The barium salt of the compound had a molecular formula, $\text{C}_{20}\text{H}_{22}\text{O}_{12}\text{N}_8\text{P} \cdot 0.5\text{Ba}$, and consumed 1.8 moles of periodate, which further confirm the structure assignment. As expected the product was resistant to venom 5'-nucleotidase.

Further proof of the structure was obtained by comparison of the product with authentic samples of diinosine phosphate, which was prepared by two methods. The first method involves the reaction of *p*-nitrophenyl phosphorodichloridate (IV)⁴ with I in pyridine and hydrolytic removal of the protective groups. III was isolated in 31% yield. The second method involves the condensation of 2',3'-di-O-acetylinosine (VII) with 2',3'-di-O-acetylinosine 5'-phosphate pyridinium salt (VIII) by the aid of dicyclohexylcarbodiimide⁵ followed by deacetylation with sodium ethoxide. VII was prepared from 5'-tritylinosine (V) by acetylation to diacetate (VI) and subsequent detritylation. VIII was synthesized by acetylation of inosine 5'-phosphate pyridinium salt with acetic anhydride in pyridine.

(1) P. A. Levene and R. S. Tipson, *J. Biol. Chem.*, **111**, 313 (1935).

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(4) A. F. Turner and H. G. Khorana, *ibid.*, **81**, 4651 (1959).

(5) P. T. Gilham and H. G. Khorana, *ibid.*, **80**, 6212 (1958).