11β,17α-dihydroxy-3,20-dioxo-4-pregnen-21-al (**14**) with 0.5 M CH_2Cl_2 as a solvate: TLC (silica gel, ether) R_f 0.23; IR (KBr) 3500 (w), 3400 (m, OH) and 1655 and 1635 cm^{-1} (s, C=O); NMR ($CDCl_3$) δ 9.77 (s, 1, CH=O), 6.1–5.7 (m, 1, OH), 5.73 (s, 1, O=CCH=C), 5.31 (s, 1, CH_2Cl_2), 4.6–4.35 (m, 1, CHO), 1.5 (s, 3, CH_3C), 1.37 (s, 3, CH_3C), and 2.8–0.85 (m, 17, CH, CH_2, and 1, OH); UV (CH_3OH) λ_{max} 242 nm (ε 17 000) and 278.5 nm (ε 13 300); $[\alpha]^{25}_D$ +117.7° (c 0.95, dioxane); mass spectrum (*m/e*) 359 ($M^+ - 1$).

Anal. Calcd for $C_{21}H_{28}O_5 \cdot 0.5CH_2Cl_2$: C, 64.08; H, 7.25. Found: C, 64.30; H, 7.15.

The NMR and mass spectra of the crude product were identical with those of the pure aldehyde as its solvate except for the presence of the singlet at δ 5.31 in the NMR spectrum due to CH_2Cl_2.

Registry No.—**1**, 34332-34-8; **2**, 13542-30-8; **7**, 66777-47-7; **8**, 66777-48-8; **9**, 55388-47-1; **10** isomer 1, 66777-49-9; **10** isomer 2, 66777-50-2; **11**, 66777-51-3; **12**, 66777-52-4; **13**, 20287-97-2; **14**, 14760-49-7; **15**, 66777-53-5; **16**, 66777-54-6; **17**, 66777-55-7; **18**, 66777-56-8; **19**, 66777-57-9; hydrocortisone, 50-23-7; 2,2-dimethoxypropane, 77-76-9; 2,2-diethoxypropane, 126-84-1; 1,1-diethoxyethane, 105-57-7; hydrocortisone 21-acetate, 50-03-3; prednisolone, 50-24-8.

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(10) Dimethylketals undergo hydrolysis faster than diethyl ketals: J. W. Taft, Jr., *J. Am. Chem. Soc.*, **74**, 3120 (1952). Further, R. Gardi et al.[2] suggested that the use of diethyl acetals and ketals is a milder reagent to effect acetalization than that of Nussbaum et al.[6]
(11) The fact that the acetonide **1** does not undergo further exchange at the 11β position while hydrocortisone 21-acetate and 11β-hydroxy-21-ethoxy-20,21-ethylidenedioxy-4,17(20)-pregnadien-3-one do suggests that the substituents on the dihydroxyacetone side chain affect the reactivity of the 11β-hydroxy: R. Gardi, R. Vitali, G. Falconi, and A. Ercoli, *J. Med. Chem.*, **15**, 556 (1972).
(12) These results are consistent with **10** being a mixture of two geometrical isomers.

Acid-Catalyzed Addition of Secondary Phosphines to Vinyl Ethers

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Although certain olefins with electron-withdrawing substituents (e.g., acrylonitrile[1] or alkyl acrylates[2]) add P–H bonds without catalysts, phosphine addition to double bonds normally requires radical initiation,[3,4] or an acidic or basic catalyst.[4] Because of the relatively high basicity of substituted phosphines, the acid-catalyzed reactions require nearly stoichiometric amounts of acid and do not proceed to tertiary phosphines.[5] We have found, however, that vinyl ethers add secondary phosphines in the presence of catalytic amounts of acid to yield the tertiary phosphine (Markownikoff product) in good yields.

Results and Discussion

Heating a mixture of di-*tert*-butylphosphine and methyl vinyl ether without added catalyst to above 130 °C yields after several hours di-*tert*-butyl(1-methoxyethyl)phosphine, a product unexpected from base- or radical-catalyzed reactions.[4] In fact, adding catalytic amounts (<5 mol %) of acid to the mixtures greatly reduces the reaction time. Similarly, diethylphosphine reacts with methyl vinyl ether and acid to yield diethyl(1-methoxyethyl)phosphine (eq 1).

$$(C_2H_5)_2PH + CH_2CHOCH_3 \xrightarrow{H^+} (C_2H_5)_2PCH(CH_3)OCH_3 \quad (1)$$

$$(C_2H_5)_2PH + CH_2CHOCH_3 \xrightarrow{AIBN} (C_2H_5)_2PCH_2CH_2OCH_3 \quad (2)$$

Using the same reagents (diethylphosphine and methyl vinyl ether) and a radical initiator, the reaction is regioselective for the *opposite* addition product, diethyl(2-methoxyethyl)phosphine (eq 2). However, attempts to perform this reaction with di-*tert*-butylphosphine gave no addition, except for slow formation of the Markownikoff product. (The expected product, di-*tert*-butyl(2-methoxyethyl)phosphine, was prepared by another method for characterization. It is a stable compound under workup and distillation conditions, with a VPC retention time different from that of the 1-methoxyethyl isomer, and would have been detected by VPC and NMR had it been present.) Although reasons for the failure of $[(CH_3)_3C]_2PH$ to add to the olefin by a radical process are not clear, steric hindrance may contribute to the unreactivity of the $[(CH_3)_3C]_2P\cdot$ radical ($[(CH_3)_3C]_2CH\cdot$ is a persistent radical[6]).

The ability of vinyl ethers to react by an acid-catalyzed process in the presence of strongly basic secondary and tertiary alkyl phosphines[7] contrasts with the behavior reported for other olefins;[5] this reaction appears to be more closely related to the acid-catalyzed addition of phosphines to aldehydes,[8,9] which proceeds through the tertiary phosphine to a quaternary phosphonium salt, $[(RCHOH)_4P]X$. The character of the oxygen-stabilized carbonium ion intermediate in our proposed mechanism (eq 3) reflects this similarity.

$$BH^+ + CH_2{=}CHOR \rightleftharpoons B + CH_3CH^+OR \xrightarrow{R'_2PH} R'_2PC(CH_3)HOR + BH^+ \quad (3)$$

$$B = R'_2PH, R'_2PC(CH_3)HOR$$

Experimental Section

Di-*tert*-butylphosphine[10,11] and diethylphosphine[12] were prepared by literature methods. These compounds and the products are air sensitive and were handled under an atmosphere of prepurified N_2. ^1H NMR spectra were recorded on a Varian EM-360A instrument. Vapor-phase chromatographic analyses were performed on a Hewlett-Packard 5840 instrument using 20 in. × ⅛ in. UCW-982 on Chromosorb W columns. Carbon–hydrogen analyses were performed in the Union Carbide Analytical Section by Mr. J. T. Hildebrand; satisfactory analyses were obtained on methiodide and $PtCl_2$ derivatives of all of the products. Methiodide derivatives were prepared by adding an acetone solution of methyl iodide to an acetone solution of the phosphine; the product crystallizes after several hours. Platinum(II) derivatives of the formula $PtCl_2(phosphine)_2$ were prepared by stirring the phosphine with Na_2PtCl_4 or $PtCl_2(NCC_6H_5)_2$ in methanol and crystallizing the product from CH_2Cl_2–methanol.

Reactions of Di-*tert*-butylphosphine with Methyl Vinyl Ether, with and without Acid. Two NMR tubes, one containing about 0.02 g of CF_3CO_2H (0.18 mmol), were charged with 0.3 g of di-*tert*-butylphosphine (2.1 mmol) and about 0.4 mL of methyl vinyl ether (9 mmoles) was condensed into each. The contents were frozen and the tubes were flame-sealed under vacuum. NMR spectra were recorded both before and after heating at 130 °C for 30 min. The tube without added acid showed no discernible reaction; the tube with acid exhibited about 70% conversion to di-*tert*-butyl(1-methoxyeth-

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yl)phosphine. The tubes were opened, and VPC analyses confirmed these results.

Reactions of Di-*tert*-butylphosphine with Methyl Vinyl Ether, with and without AIBN. Two NMR tubes, one containing 0.05 g of AIBN (0.3 mmol), were charged with 0.3 g of di-*tert*-butylphosphine (2.1 mmol) and about 0.4 mL of methyl vinyl ether (9 mmol) was condensed into each. The contents were freeze–thaw–degassed and the tubes were sealed under vacuum. Both were heated at 80 °C for 5 h; no reaction was observed by NMR. The temperature was then raised to 140 °C, and after 4 h at this level a reaction was beginning in the tube without AIBN. After 18 h more, this reaction had gone to completion, yielding di-*tert*-butyl(1-methoxyethyl)-phosphine. The reaction in the other tube was also yielding the same product, but was less than 50% complete. A reaction at 140 °C with di-*tert*-butyl peroxide in place of AIBN gave similar results.

Di-*tert*-butyl(1-methoxyethyl)phosphine. An excess of methyl vinyl ether (4 mL, 90 mmol) was condensed into a heavy-walled glass tube containing a mixture of 4.0 g of di-*tert*-butylphosphine (27 m moles) and 0.1 mL of trifluoroacetic acid (0.6 mmol). The contents were frozen and the tube was flame-sealed under vacuum, then heated to 130 °C for 1.5 h. The contents were distilled (bp 54–56 °C (0.4 mm)) to give 3.38 g (60%) of the product: ^{1}H NMR (neat) δ 1.15 (d, $^3J_{PH}$ = 10.5 Hz, 9 H, $C(CH_3)_3$), 1.22 (d, $^3J_{PH}$ = 10.5 Hz, 9 H, $C(CH_3)_3$, diastereotopic *tert*-butyl groups), 1.45 (d of d, $^3J_{HH}$ = 7 Hz, $^3J_{PH}$ = 15 Hz, 3 H, CH_3), 3.20 (s, 3 H, OCH_3), 3.72 (q of d, $^3J_{HH}$ = 7 Hz, $^2J_{PH}$ = 3 Hz, 1 H, CH).

Diethyl(1-methoxyethyl)phosphine. Excess methyl vinyl ether (4 mL, 90 mmol) was condensed onto a mixture of 2.0 g of diethylphosphine (22 mmol) and 0.05 mL of CF_3CO_2H (0.3 mmol) in a heavy-walled glass tube. The tube was then sealed, heated at 130 °C for 3 h, cooled, and opened. Vacuum distillation (bp 90–93 °C (40 mm)) gave 2.3 g (70%) of the product: ^{1}H NMR ($CDCl_3$) δ 0.7–1.7 (m, 13 H, CH_2CH_3 and CH_3), 3.38 (s, 3 H, OCH_3), 3.55 (m, 1 H, CH).

Di-*tert*-butyl(2-methoxyethyl)phosphine. A solution of $[(CH_3)_3C]_2PLi$[13] in 120 mL of THF (distilled from $LiAlH_4$) was prepared from 7.85 g of di-*tert*-butylphosphine (53.8 mmol) and 37 mL of 1.8 M phenyllithium solution (66 mmol). To this was added 6.5 g (69 mmol) of 2-chloroethyl methyl ether[14] (prepared from 2-methoxyethanol, thionyl chloride, and pyridine) in 50 mL of THF. The mixture was stirred for 1 h, and then 5 mL of methanol was added. Solvents were removed by distillation at atmospheric pressure, leaving a thick mixture. About 30 mL of ethyl ether was added; the suspension was filtered, washed with 100 mL of H_2O, and dried over $MgSO_4$. Vacuum distillation (bp 65–70 °C (0.15 mm)) gave 6.55 g (60%) of the product: ^{1}H NMR ($CDCl_3$) δ 1.22 (d, $^3J_{PH}$ = 11 Hz, 18 H, $(CH_3)_3C$), 1.70 (m, 2 H, PCH_2), 3.30 (s, 3 H, OCH_3), 3.50 (m, 2 H, OCH_2).

Diethyl(2-methoxyethyl)phosphine. Excess methyl vinyl ether (1.5 mL, 34 mmol) was condensed into a mixture of 0.95 g of diethylphosphine (11 mmol) and 0.10 g of AIBN (0.6 mmol) in a heavy-walled glass tube. The tube was sealed and heated at 80 °C for 2 h. Vacuum distillation (bp 96–99 °C (40 mm)) of the contents gave 0.98 g (64%) of the product: ^{1}H NMR ($CDCl_3$) δ 0.7–1.5 (m, 10 H, CH_2CH_3), 1.6 (m, 2 H, PCH_2), 3.35 (s, 3 H, OCH_3), 3.50 (overlapping triplets, $^3J_{HH}$ and $^3J_{PH}$ = 8 Hz, 2 H, OCH_2).

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Registry No.—Di-*tert*-butylphosphine, 819-19-2; methyl vinyl ether, 107-25-5; di-*tert*-butyl(1-methoxyethyl)phosphine, 66792-96-9; diethyl(1-methoxyethyl)phosphine, 66792-97-0; diethyl phosphine, 627-49-6; di-*tert*-butyl(2-methoxyethyl)phosphine, 66792-98-1; *t*-Bu_2PLi, 19966-86-0; 2-chloroethyl methyl ether, 627-42-9; diethyl(2-methoxyethyl)phosphine, 66792-99-2.

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Stereochemistry of the Photoinduced Addition of Methanol to Pummerer's Ketone, a 2-Cyclohexenone

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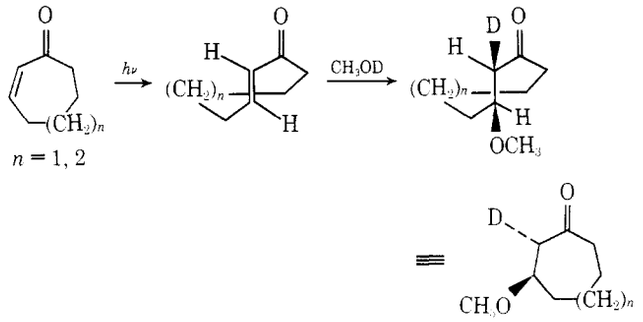
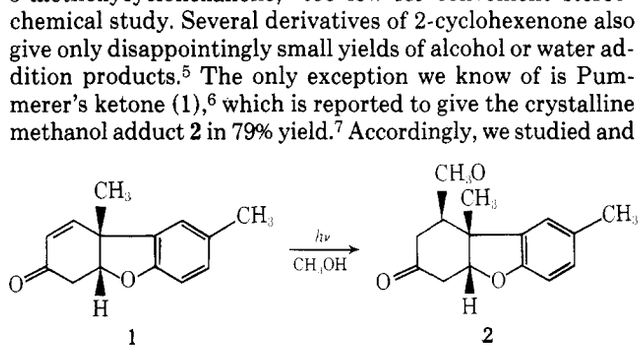
By using methanol-*d*, we recently showed that the photoinduced addition of methanol to 2-cycloheptenone, 2-cyclooctenone, and related compounds involves two steps: (a) photoisomerization to the *trans*-cycloalkenone, and (b) regio- and stereospecific syn addition of methanol to the ground state trans ketone.[1,2]



It was desirable to extend these studies to a 2-cyclohexenone, where photoisomerization to a trans ketone presumably would be more difficult.[3] Unfortunately, irradiation of 2-cyclohexenone itself in methanol gives only a 0.7% yield of 3-methoxycyclohexanone,[4] too low for convenient stereochemical study. Several derivatives of 2-cyclohexenone also give only disappointingly small yields of alcohol or water addition products.[5] The only exception we know of is Pummerer's ketone (1),[6] which is reported to give the crystalline methanol adduct **2** in 79% yield.[7] Accordingly, we studied and



1 2

report here the stereochemistry of this reaction with CH_3OD, and also the isotope effect for the addition.

Results

Although we confirm the overall stereochemical assignment[7] of the methoxyl and angular methyl in **2** as being cis, we find some discrepancies in the previous[7] proton NMR assigments. Since the correct assignments, particularly those for H_D and H_E, were essential for establishing the stereochemistry of CH_3OD addition, we examined the 180 MHz proton spectrum of **2** in detail. The results, with the previous and new assignments, are given in Table I. The previous assignments of H_D and H_E should be reversed, as should those

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