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Application of the Wittig Reaction to the Synthesis of Steroidal Side Chains. Possibility of 3β-Phenoxy Formation as a Secondary Reaction

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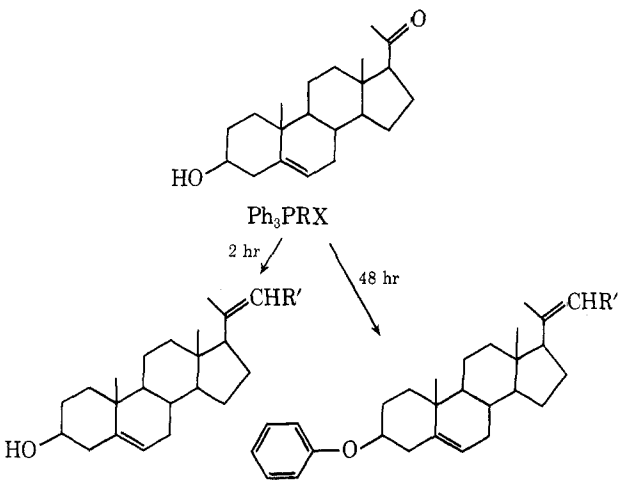
The Wittig reaction of various alkylidenephosphoranes with Δ^5-pregnen-3β-ol-20-one has been studied. The formations of 3β-phenoxy derivatives in a secondary reaction is demonstrated.

With the available methods for the synthesis of side-chain steroids from C-20 and C-21 compounds, one obtains stereoisemeric 20-hydroxy compounds as an intermediate.[1] The latter, on being dehydrated at C-20 and then catalytically hydrogenated, yield a mixture of the two possible isomers. The dehydration of a 20-hydroxy intermediate in principle could give five different olefins: two $\Delta^{17(20)}$-dehydro compounds, the corresponding $\Delta^{20(21)}$ isomer, and two $\Delta^{20(22)}$ isomers.[2,3,4] The isomerism difficulty was partially resolved by Sondheimer and Mechoulam[5], who described the synthesis of $\Delta^{5,20(21)}$-cholestadien-3β-ol acetate by use of the Wittig reaction on 21-nor-20-ketocholesteryl acetate followed by hydrogenation. Subsequently, the Wittig reaction was applied, principally with triphenylphosphine methylene reagent,[6] to various keto steroids. In order to develop a simple route to various unambiguous isomeric side chain steroids, we investigated the Wittig reaction with Δ^5-pregnen-3β-ol-20-one (pregnenolone).

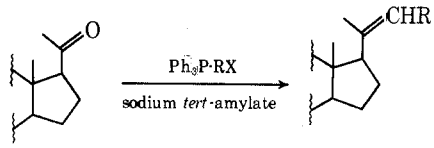
In the first study, isopentylidenephosphorane as the Wittig reagent in the presence of sodium *tert*-amylate[7] as base in benzene solution was found to give the $\Delta^{5,20(22)}$-cholestadien-3β-ol. Thin layer chromatography on Kieselgel with benzene as eluent revealed two products. The faster moving material, with a 0.9 R_f, was present in very low yield after the usual Wittig reaction time. The slower moving component, with a 0.6 R_f, isolated in 80% yield, was found to be the desired $\Delta^{5,20(22)}$-cholestadien-3β-ol. The fast-moving compound, which was initially present in negligible quantities, became the predominant compound with a longer reaction time. The ir spectrum of this secondary product shows the presence of bands at 1598, 1584, 1241, 760, and 694 cm^{-1}. NMR spectroscopy revealed two multiplets appearing respectively at 6.92 and 7.28 ppm. In comparison with the cholesterol the 3β proton was shifted 0.5 ppm to higher field and the 19 methyl peak was shifted 0.02 ppm to lower field. Protons H-6 and H-22 exhibited no observable shift change. Finally, mass spectroscopy gives a molecular ion at 76 units above the expected mass and a base peak 93 units lower than the molecular ion. All of these data support the replacement of the 3β-hydroxyl group by a 3β-phenoxy group in the minor product.



We have also carried out this reaction in the presence of cholesterol and triphenylphosphonium salt and obtained, in either benzene or toluene as solvent, 3β-phenoxycholesterol in high yield. As expected, no substitution occured when the phosphonium salt was absent.

The normal acetylated 20(22) condensation product was then selectively hydrogenated[8] in dioxane, in the presence of acetic acid and platinum oxide as catalyst, to give (80% yield) a product which was identical with the natural product in its spectroscopic properties, melting point, and specific rotation, $[\alpha]^{20}D$ −39.5° ($CHCl_3$). No other hydrogenated product was isolated. This selectivity results from two principal reasons. First, the Wittig reaction on pregnenolone gives a single condensation product (TLC proof and precise melting point, 124.5 ± 0.5°), which was found to be the 20(22) *E* isomer as evidenced by its 18-methyl NMR

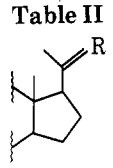
Table I



Phosphorane R	Registry no.	Products R'	3β-Acetate[c] Yield, %	3β-Acetate[c] Mp, °C	3β-Phenoxy[b,d] Mp, °C
CH_3	3487-44-3	H	87	130.5 ± 0.5	
C_2H_5	1754-88-7	CH_3	75	155 ± 1	105 ± 1
C_3H_7	16666-78-7	C_2H_5	82		106 ± 1
C_4H_9	3728-50-5	C_3H_7	79	111.5 ± 0.5	95 ± 1
C_4H_9-i[a]	21960-27-0	C_3H_7-i[a]	67	109 ± 1	
C_5H_{11}	29541-98-8	C_4H_9	73	115.5 ± 0.5	82 ± 1
C_5H_{11}-i[a]	39110-24-2	C_4H_9	84	126 ± 1	98.5 ± 0.5
C_6H_{13}	16666-79-8	C_5H_{11}	78	104.5 ± 0.5	60 ± 1
C_6H_{13}-i[a]	54517-55-4	C_5H_{11}-i[a]	80	124.5 ± 0.5	96 ± 1

[a] Isoterminal group. [b] 3β-Phenoxycholesterol: mp 151 ± 1°. Yields of 3β-phenoxy compounds are about 85% after 48 hr of reaction time. [c] Registry no. are, respectively, 38388-16-8, 54517-67-8, 54548-86-6, 54517-66-7, 54517-65-6, 54517-64-5, 54517-63-4, 54548-85-5. [d] Registry no. are, respectively, 54517-62-3, 54517-61-2, 54517-60-1, 54517-59-8, 54517-58-7, 54517-57-6, 54517-56-5.

Table II



R	Side chain 20(22) effect[b] 18-Me	21-Me	22-H
$=CH_2$	0.59	1.76	4.72 + 4.86
$=CHCH_3$	0.55	1.63	5.27
$=CHC_2H_5$	0.55	1.63	5.26
$=CHC_3H_7$	0.55	1.63	5.20
$=CHC_3H_7$-i[a]	0.55	1.63	5.20
$=CHC_4H_9$	0.55	1.63	5.20
$=CHC_4H_9$-i[a]	0.55	1.63	5.20
$=CHC_5H_{11}$	0.55	1.63	5.20
$=CHC_5H_{11}$-i[a]	0.55	1.63	5.20
Cholesterol	0.68	0.92	

[a] Isoterminal group. [b] All shifts are given in parts per million relative to TMS.

shift.[9] This result is probably due to the fact that the ratio of geometric isomers in the olefinic product appears to be controlled by a combination of steric factors in the reactants and by environmental factors.[10] In a nonpolar solvent such as benzene, the reactants probably approach in the first step of the reaction, to give the threo form as an intermediate which possesses maximum electrostatic attraction and minimum nonbonded interaction between the eclipsed substituents, and the thermodynamically more stable *E* isomer predominates after cis elimination in the second reaction step.

Second, with consideration for the steric hindrance of the condensation product, we have made a mathematical computer model[11] of the product and, on varying the two dihedral angles [PHI (1) 17–17–20–22 and PHI (2) 20–22–23–24], have found two preferential conformations: the first with PHI (1) = 170° and PHI (2) oscillating between 70 and 310° and the second with PHI (1) = 320° and the same PHI (2) as the first. We must note an energetic predominance of the 320° PHI (1) position, which corresponds to an α-21-methyl. Examination of the model also shows that on steric grounds only the α side is capable of being absorbed on the catalyst surface, near the 20(22) olefinic bond. Further, rotation of the side chain during the hydrogenation is sterically improbable. Reaction of pregnenolone with a series of different phosphoranes for 2 hr gave only the expected addition product, whereas extension of the time to 48 hr resulted in formation of the 3β-phenoxy derivatives (Table I). The NMR spectra of the products exhibit an important shift of about 0.7 ppm toward low field for the 21-methyl and a 0.12-ppm shift toward high field for the 18-methyl, when compared with compounds having a saturated side chain. A broad one-proton triplet at 5.2 ppm corresponds to the H-22 proton. 3β-Acetates exhibit a singlet at 1.03 ppm (19-methyl) and a broad multiplet centered at about 4.6 ppm (H-3) whereas in 3β-phenoxy compounds the 19-methyl peak appears at 1.05 ppm and the 3 H proton multiplet is centered at 4.1 ppm (Table II).

Experimental Section

Melting points are uncorrected. Infrared spectra were recorded on KBr disks, with a Beckman IR-12 double beam spectrophotometer. NMR spectra were measured in $CDCl_3$ solution, with Me_4Si as reference at room temperature, on a 60-MHz EM-360 Varian NMR spectrometer and at 100 MHz on an XL-100 Varian NMR spectrometer with external H_2O lock.

$\Delta^{5,20(22)}$-Cholestadien-3β-ol Acetate (Typical Reaction). Isopentylidenephosphorane (17.8 mmol) in 12 ml (1.5 mol) of sodium *tert*-amylate was refluxed under nitrogen during 15 min. To the dark-red solution was quickly added 3.2 mmol of pregnenolone in 15 ml of hot benzene solution. The combined solution was gently refluxed for 2 hr. The solution was cooled, filtered over crushed ice, acidified with 2 *N* hydrochloric acid, and extracted with ether. The organic layer was washed with water and dried over anhydrous Na_2SO_4 and the ether was evaporated. The residue was acetylated by being allowed to stand overnight with 20 ml of pyridine and 20 ml of acetic anhydride. Extraction with ether in the usual way led to a product which was isolated by preparative thin layer chromatography (2-mm thickness Kieselgel, Merck), yield 80%, mp 124.5 ± 0.5°. The analytical sample was obtained by crystallization from methanol. All the other Wittig condensation products were obtained as described above.

Cholesterol Acetate from $\Delta^{5,20(22)}$-Cholestadien-3β-ol Acetate. The diene (1 g, 2.3 mmol) of 50 ml of pure dioxane and 1 ml of glacial acetic acid was hydrogenated in the presence of 0.1 g of reduced platinum oxide, at room temperature and atmospheric pressure, until the theoretical quantity of hydrogen was absorbed. The filtered solution was diluted with water, extracted with ether, washed with water, and dried over anhydrous Na_2SO_4. After the ether was removed, the crude product was recrystallized in CH_3OH–$CHCl_3$ (1:1) solution, isolated 1.88 mmol, yield 80.5%, $[\alpha]^{20}D$ −31.5° ($CHCl_3$).

Registry No.—Pregnenolone, 145-13-1.

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Total Synthesis of (±)-6,7-Didehydroaspidospermine

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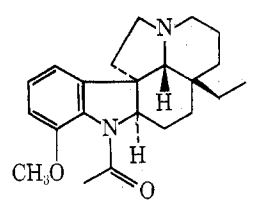
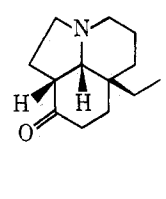
The total synthesis of the indole alkaloid derivative (±)-6,7-didehydroaspidospermine (**5**) by a Fischer indole approach is described. The cyclization precursor **4** was prepared in a stepwise fashion from ethyl 2-formylbutyrate via the key intermediates **10, 14, 16, 21,** and **6**. Upon heating in acetic acid the *o*-methoxyphenylhydrazone of **4** was cyclized to indolenine **27,** which on reduction and acetylation afforded (±)-6,7-didehydroaspidospermine (**5**).

Some years ago a total synthesis of the indole alkaloid aspidospermine (**1**) was developed in these laboratories by Stork and Dolfini.[2,3] This synthesis possessed as its main feature the construction of tricyclic amino ketone **2** and the subsequent Fischer indole cyclization of its *o*-methoxyphenylhydrazone. We became intrigued with the possibility that this approach might be extended to provide a route to 6,7-didehydro indole alkaloids, e.g., the pharmacologically important alkaloids vindoline (**3a**)[4] and vindorosine (**3b**).[5]



1



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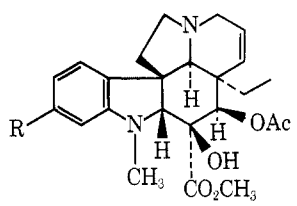
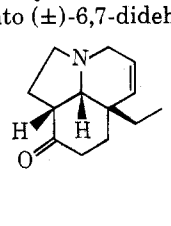


3a, R = OCH_3
b, R = H

We wish to report here a synthesis of the required unsaturated tricyclic amino ketone **4** and its subsequent conversion into (±)-6,7-didehydroaspidospermine (**5**).



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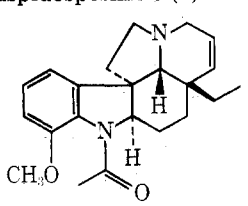
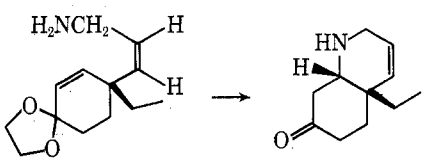


5

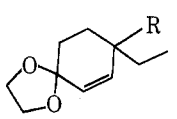
The synthetic plan involved construction of the necessary bicyclic amino ketone **6** by the hydrolysis and subsequent cyclization of ketal cis-allylic amine **7**. The third ring



7 **6**

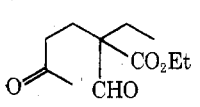
of unsaturated tricyclic amino ketone **4** could then be introduced in the same manner used in the preparation of the saturated analog **2**.[2]

It was decided to build up the cis-allylic amine chain of **7** in a stepwise manner from ketal ester **8**. Michael addition

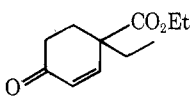


8, R = CO_2Et
11, R = CH_2OH
12, R = CHO
13, R = CH=CHCl
14, R = C≡CH
15, R = C≡CCH_2OH

of ethyl 2-formylbutyrate[6] to methyl vinyl ketone gave adduct **9**, which was cyclized with piperidine acetate–acetic acid in refluxing benzene[7] to afford cyclohexenone ester **10**



9



10

in 73% yield. Ketalization gave a quantitative yield of the desired ketal ester **8**.

The ketal ester **8** was then reduced with lithium aluminum hydride (ether, 0°, 4 hr) to give ketal alcohol **11** in 57%