n^{20}D 1.4544; yield 19.3 g (71%); δ_{31P} 3.2 ppm. Anal. Calcd for $C_8H_{15}NO_5PCl$: C, 35.40; H, 5.54; P, 11.40. Found: C, 35.11; H, 5.89; P, 11.06.

***O,O*-Diethyl 1-(*N*-Ethoxycarbonylamino)-1-methylethylphosphonate (4a).** To a solution of phosphonate **1b** (13.6 g, 0.05 mol) in ethyl ether (300 ml) a solution of MeMgI (0.15 mol) in ether (100 ml) was dropped with vigorous stirring while maintaining the temperature at −10 °C. Stirring was continued until the temperature rose to 15 °C after which the mixture was cooled to −5 °C and a saturated solution of ammonium chloride in water (60 ml) was carefully added. The organic layer was separated and the aqueous phase extracted with chloroform (2 × 40 ml). The combined organic layers were dried over anhydrous magnesium sulfate, the solvent evaporated, and the oily residue distilled, bp 93–94 °C (0.05 mm), n^{20}D 1.4505, yield 8.4 g (63%).

Anal. Calcd for $C_{10}H_{22}NO_5P$: C, 44.90; H, 8.25; P, 11.61. Found: C, 45.22; H, 8.05; P, 11.40.

Reaction of Phosphonate 1b with Isopropylmagnesium Iodide. To a solution of isopropylmagnesium iodide (0.075 mol) in ethyl ether (150 ml) a solution of phosphonate **1a** (6.8 g, 0.025 mol) in ether (30 ml) was dropped with vigorous stirring while keeping the temperature at −10 °C. Stirring was continued until the temperature rose to 15 °C and after cooling to −5 °C the mixture was worked up as described for the case of **4a**. The crude phosphonate was identified as **4d** and was hydrolyzed without purification according to the procedure described by Chambers and Isbell, yielding 1.7 g (44%) of 1-aminoisobutylphosphonic acid **2d**.

***O,O*-Diethyl 1-(*N*-Ethoxycarbonylamino)-1-thioethylalkylphosphonates (3b–e).** To a solution of alkylmagnesium iodide (0.05 mol) (MeI, EtI, *i*-PrI, $PhCH_2Cl$) in ethyl ether (200 ml), a solution of phosphonate **1a** (7.5 g, 0.025 mol) in ether (30 ml) was dropped with vigorous stirring while keeping the temperature at −10 °C. Stirring was continued until the temperature rose to 15 °C and after cooling to −5 °C the mixture was worked up as described above for the case of **4a** except that the crude product obtained after the evaporation of solvent was used directly in the next step.

***O,O*-Diethyl 1-(*N*-Ethoxycarbonylamino)alkylphosphonates (4b–e).** Solutions of the crude phosphonates **3b–e** (prepared from 0.025 mol of **1a**) in THF (70 ml) were refluxed with sodium borohydride (1.5 g, 0.04 mol) for 2 h. After cooling to 20 °C, water (30 ml) was carefully added. The organic layer was separated, the water layer extracted with chloroform (3 × 30 ml), and the combined extracts dried over anhydrous magnesium sulfate. After evaporation of solvent the crude phosphonates **4b–e** were hydrolyzed without purification.

1-Aminoalkylphosphonic Acids (2a–e). Hydrolysis of phosphonates **4a–e** and isolation of the corresponding aminophosphonic acids **2a–e** was carried out according to the procedure described by Chambers and Isbell.[7] For the results see Table I.

1-(*N*-Ethoxycarbonylamino)ethyldiphenylphosphine Oxide (7). A solution of phosphine oxide **6**[3] (7.2 g, 0.02 mol) in THF (70 ml) was refluxed with sodium borohydride (1.5 g, 0.04 mol) for 2 h. After cooling to 20 °C, water (30 ml) was carefully added. The organic layer was separated and the aqueous phase extracted twice with chloroform (2 × 30 ml). The combined organic layers were dried over anhydrous magnesium sulfate and the solvent evaporated. The oily residue crystallized upon adding a small amount of ethyl ether. The product was filtered and recrystallized from benzene–petroleum ether (2:1) to give 5.5 g (87%) of **7**, mp 146–147 °C, δ_{31P} −35.0 ppm. Anal. Calcd for $C_{17}H_{20}NO_3P$: C, 64.30; H, 6.32; P, 9.78. Found: C, 64.37; H, 6.46; P, 9.84.

1-Aminoethyldiphenylphosphine Oxide (8). Phosphine oxide **7** (2.0 g, 0.0063 mol) was dissolved in a solution of HBr in acetic acid (40%, 20 ml). The reaction mixture was let stand at room temperature for 3 days. The crude 1-aminophosphine oxide hydrobromide separated as an oily liquid after addition of ethyl ether (about 100 ml). The oil was dissolved in 10 ml of water and the solution extracted twice with chloroform (2 × 10 ml) in order to remove unchanged **7**. The aqueous solution was neutralized with potassium carbonate and crude **8** extracted with chloroform (10 × 10 ml). The organic layer was dried ($MgSO_4$), the solvent evaporated, and the oily residue crystallized from benzene–petroleum ether (2:1) to give 0.7 g (55%) of pure **8**.

Anal. Calcd for $C_{14}H_{16}NOP$: C, 68.60; H, 6.53; P, 12.66. Found: C, 68.42; H, 6.31; P, 12.91.

Registry No.—**1a**, 60064-40-6; **1b**, 35156-57-1; **2a**, 5035-79-0; **2b**, 6323-97-3; **2c**, 14047-23-5; **2d**, 18108-24-2; **2e**, 6324-00-1; **3b**, 60064-41-7; **3c**, 60064-42-8; **3d**, 60064-43-9; **3e**, 60064-44-0; **4a**, 60064-45-1; **4b**, 60064-46-2; **4c**, 60064-47-3; **4d**, 60064-48-4; **4e**, 60064-49-5; **6**, 59766-64-2; **7**, 60064-50-8; **8**, 60064-51-9; ethoxycarbonyl isothiocyanate, 16182-04-0; triethyl phosphite, 122-52-1; sulfuryl chloride, 7791-25-5; isopropyl iodide, 75-30-9.

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A Convenient Synthesis of 25-Oxo-27-norcholesteryl Acetate

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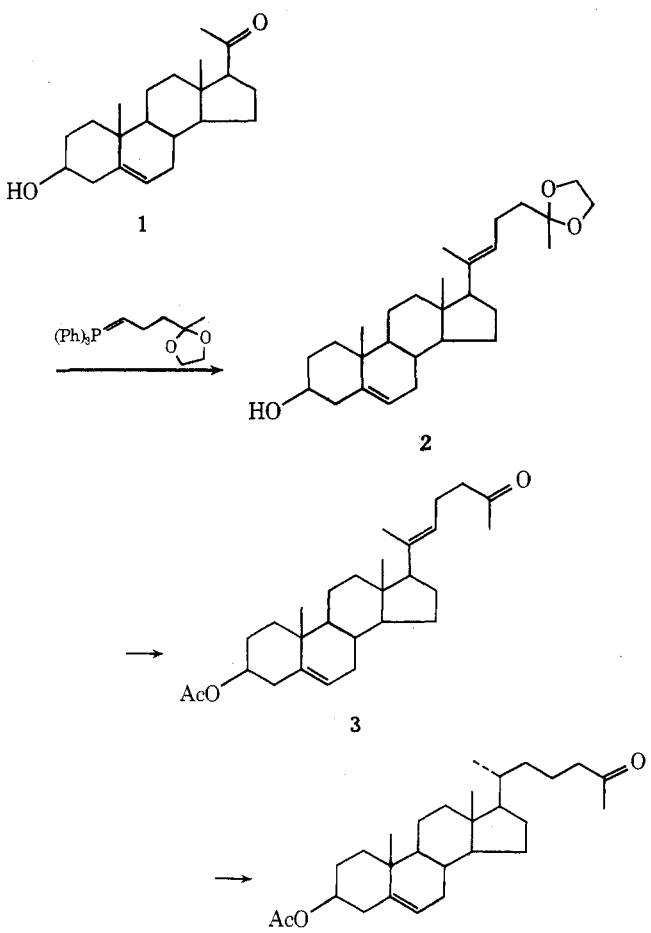
During an examination of the scope of the Wittig reaction with C-20 steroidal ketones as reported by Piraux and co-



workers[1] the synthesis of 25-oxo-27-norcholesteryl acetate, a key intermediate for the synthesis of 25-hydroxy vitamin D_3,[2-4] was undertaken. We wish to report an efficient preparation of this intermediate (4) starting from pregnenolone (1). The main steps are the Wittig reaction of pregnenolone with the ketal phosphorane shown below, and subsequent hydrogenation of the $\Delta^{20(22)}$ double bond of the product. A slightly higher overall yield can be obtained if the 3-hydroxyl is protected as the tetrahydropyranyl ether during the Wittig reaction.

The stereochemistry of the Wittig product (2) was found to be exclusively *E* as expected.[1] The NMR spectrum showed the 21-methyl as a singlet at δ 1.64 which is characteristic of the *E* isomer (lit. δ 1.65)[2] whereas the chemical shift in the *Z* isomer falls in the range δ 1.67–1.70. Deketalization and acetylation of 2 gave the keto acetate 3 which was identical with an authentic sample.[5] It was selectively hydrogenated in dioxane in the presence of acetic acid with platinum oxide as catalyst. A 90% yield of the 20*R* epimer (4) was obtained.[6] The 20*S* epimer was detected by NMR spectroscopy in the mother liquor from recrystallization of the hydrogenation product. The signal for the 21-methyl in this epimer appeared as a doublet centered at δ0.84 while that for the 20*R* epimer appeared at δ 0.94. The epimers could be separated by GLC. Their identity was confirmed by comparison with authentic samples.[5] The overall yield of 4 from pregnenolone was 62%.

Experimental Section

Melting points (uncorrected) were determined on a Köfler apparatus and NMR and ir spectra on Varian (220 MHz) and Beckman IR 18 A-X spectrometers, respectively. A Varian 2100 Aerograph was used for GLC analysis.

$\Delta^{5,20(22)}$-27-norcholestadien-3β-ol-25-one 25-Ketal (2). [3-(2-Methyl-1,3-dioxalan-2-yl)propyl]triphenylphosphonium bromide[7] (5.2 g, 11 mmol) in 5.7 ml of a benzene solution of potassium *tert*-amylate[8] (2.1M) was refluxed under argon for 45 min, then 500 mg of pregnenolone dissolved in 8 ml of hot benzene was added to the dark red solution. The combined solution was refluxed for 3 h, cooled, and poured into water and the resulting mixture extracted with ether. The ether extract was washed successively with 5% hydrochloric acid, 10% sodium bicarbonate solution, and water and dried over $MgSO_4$. Removal of the solvent and chromatography of the residue (silica gel, ethyl acetate–petroleum ether, 4:1) gave 470 mg (69%) of product: mp 139–140 °C; NMR ($CDCl_3$) δ 0.54 (s, 18-Me), 1.00 (s, 19-Me), 1.32 (s, 26-Me), 1.64 (s, 21-Me), 3.52 (m, 1 H, 3α-H), 3.97 (d, J = 1 Hz, 4 H, OCH_2CH_2O), 5.16 (t, J = 6.7 Hz, 1 H, 22-H), 5.33 (m, 1 H, 6-H). Cleavage of the ketal, by keeping a solution of the product in ethanol–water with toluenesulfonic acid for 12 h, followed by acetylation with acetic anhydride–pyridine overnight afforded $\Delta^{5,20(22)}$-27-norcholestadien-3β-ol-25-one acetate (3) in 98% yield: mp 115–118 °C (lit. 120–121 °C[2]); ir (KBr) 1740, 1720 cm^{-1}; NMR ($CDCl_3$) δ 0.53 (s, 18-Me), 1.02 (s, 19-Me), 1.64 (s, 21-Me), 2.03 (s, acetate), 2.14 (s, 26-Me), 4.59 (m, 1 H, 3α-H), 5.10 (t, J = 6.7 Hz, 22-H), 5.35 (m, 1 H, 6-H). The ir and NMR spectra were identical with those of an authentic sample.[5]

25-Oxo-27-norcholesteryl Acetate (4). The acetate 3 (300 mg) dissolved in 15 ml of dioxane–acetic acid (50:1) was hydrogenated in the presence of 30 mg of prereduced platinum oxide at room temperature and atmospheric pressure. After 4 h more platinum oxide (30 mg) was added. The reaction was complete after 7 h. The catalyst was separated by filtration and the solvent removed from the filtrate to give the crystalline product which was recrystallized from ethanol (yield 276 mg, 90%): mp 140–142 °C (lit. 139–140 °C);[2] ir (KBr) 1738, 1720 cm^{-1}; NMR ($CDCl_3$) δ 0.68 (s, 18-Me), 0.95 (d, J = 6 Hz, 21-Me), 1.02 (s, 19-Me), 2.02 (s, acetate), 2.13 (s, 26-Me), 4.61 (m, 3α-H), 5.39 (m. 6-H). The ir and NMR spectra were identical with those of an authentic sample.[5] The retention times on GLC (3% OV-17 on Gaschrom Q at 300 °C) were the same but differed from that of the 20*S* epimer.

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Registry No.—1, 145-13-1; 2, 60065-10-3; 3, 53139-44-9; 20*R*-4, 7548-94-9; 20*S*-4, 55122-55-9; 3-(2-methyl-1,3-dioxolan-2-yl)propylidenetriphenylphosphorane, 3054-93-1.

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Approaches to the Synthesis of 1,2-Cyclooctatrienedione

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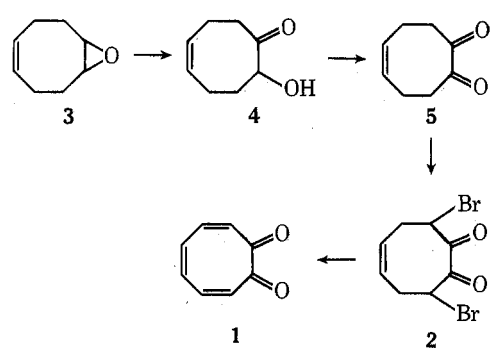
The recent interest[1-6] in the synthesis of the elusive 1,2-cyclooctatrienedione (1) and its isomers prompts this report of our successful synthesis of the quinoxaline derivative of 1 together with the chemistry of precursors to this potentially aromatic compound.

As a likely precursor to 1 a four-step synthesis of 3,8-dibromo-5-cyclooctene-1,2-dione (2) was undertaken. Epoxidation of 1,5-cyclooctadiene afforded the known[7] epoxy olefin 3 which was converted to keto alcohol 4 upon treatment with boron trifluoride in dimethyl sulfoxide. Cupric acetate oxidation of 4 gave 5-cyclooctene-1,2-dione (5) which has been prepared previously by another route.[1]

Cupric bromide dibromination of 5 resulted in the formation of 2 as a white, crystalline material. The infrared carbonyl absorptions of 2 at 1740 and 1727 cm^{-1} established[8] that the molecule exists in the trans diequatorial configuration. Confirmation of this assignment was obtained from the ^1H NMR spectrum ($CDCl_3$) which exhibits a single methine hydrogen absorption at δ 5.15 as an ABX doublet of doublets.[9]

Scheme I



3 4 5 1 2

To date all efforts to convert 2 to 1 by direct dehydrobromination have proven unsuccessful. Numerous procedures have been attempted which result in either recovered starting material or a multitude of intractable products.

Treatment of 2 with warm hexamethylphosphoric triamide,[10] however, resulted in the formation of the monodehydrobrominated product 3-bromo-5,7-cyclooctadiene-