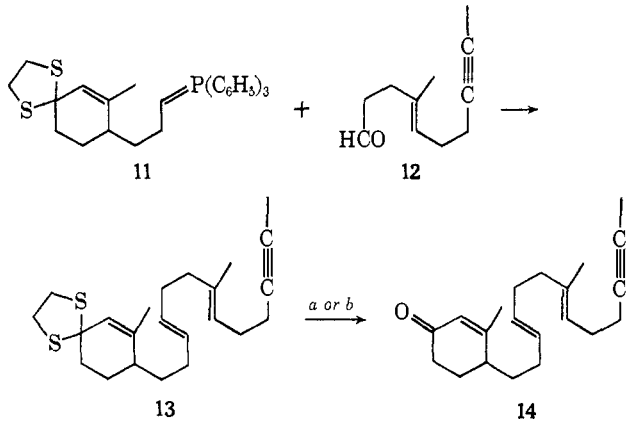
Scheme II



[a] CH_3CN–H_2O–CH_3I (10:2:1), 11 hr, 50°. [b] For optically active **13**: DMF–H_2O–CH_3I (10:2:1), $CaCO_3$, 44 hr, 22°.

distillation at 160° (0.025 mm), the ketone *dl*-**14**[6] in 93% yield (*Anal.* Found: C, 84.6; H, 10.3). For suppressing racemization during the ketal hydrolysis, buffered conditions (procedure *b*, Scheme II) were required and the yields were lower (40–50%): *d*-**14**, $[\alpha]D$ +58.4°;[9] *l*-**14**, $[\alpha]D$ −58.0°.[9] The *dl*, *d*, and *l* forms of the allylic alcohol **1**[6] were obtained as a mixture of C-2 epimers in quantitative yield by reduction of the various forms of **14** with excess sodium bis(2-methoxyethoxy)aluminum hydride in tetrahydrofuran (2 hr, 0°). A sample of *dl*-**14** was chromatographed on basic alumina (*Anal.* Found: C, 84.0; H, 10.5). The cyclization of the various forms of **1** and proof of structure and configuration of the products are disclosed in the accompanying communication.[4]

Acknowledgment. We are indebted to the National Institutes of Health and the National Science Foundation for support of this research.

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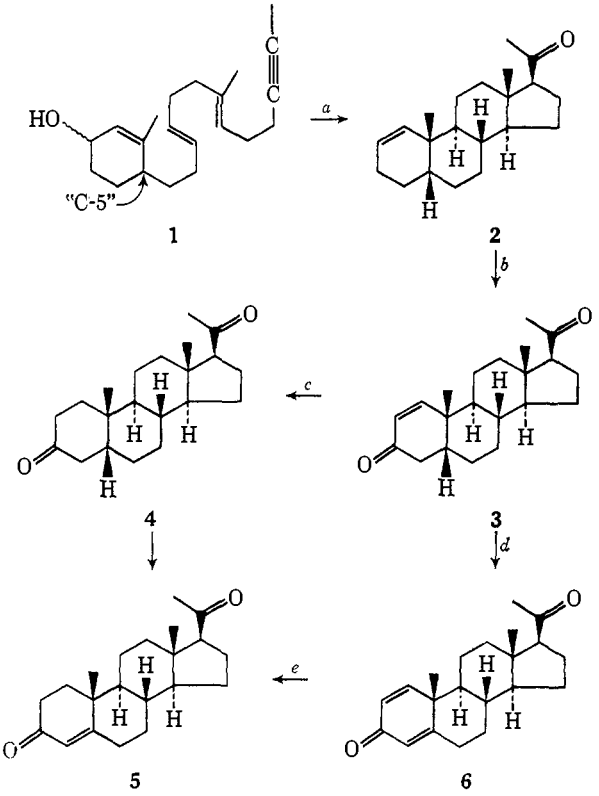
Direct Formation of the Steroid Nucleus by a Nonenzymic Biogenetic-Like Cyclization. Cyclization and Proof of Structure and Configuration of Products

Sir:

In a companion paper,[1] we have disclosed the synthesis of the trienynol **1** in its *dl*, *d*, and *l* forms (as a mixture of C-2 epimers, but essentially optically pure with respect to C-5). The present paper describes the cyclization of these stereoisomers, and the proof of structure and configuration of the products. In the course of this study a totally synthetic pathway to optically active progesterone (**5**) has been realized.

The various forms of the crude alcohol **1** were cyclized as described for a related case[2] except that 1,1-difluoroethane was employed as the solvent (see Scheme I). The reaction mixture was maintained at

Scheme I



[a] CF_2HCH_3, 12% ethylene carbonate, 8% CF_3CO_2H, 1.5 hr, −25°. [b] 7.0 mol equiv of *tert*-butyl chromate, $CCl_2{=}CCl_2$, HOAc, Ac_2O, 50 min, 100°. [c] H_2, 10% Pd/C. [d] 1.5 mol equiv of DDQ, 2 mol equiv of $C_6H_5CO_2H$, toluene, 4 hr, 120°. [e] $Rh(PPh_3)_3I$, toluene–ethanol (1:1), H_2.

reflux (−25°) for 1.5 hr before being quenched with alkali. Chromatography on Florisil gave a 65% yield of Δ^1-5β-pregnen-20-one (**2**)[3] as an 85:15 mixture of the 17β:17α epimers (shown by vpc). Crystallization from methanol–ethyl acetate afforded the 17β epimer: *dl*-**2**, mp 102.5–103.5°, mass spectrum *m/e* 300 (M^+); *d*-**2**, mp 89.5–90.5°, $[\alpha]D$ +178°[4] (optical purity 100%; see below); *l*-**2**, mp 89.5–90.5°, $[\alpha]D$ −177°.[4] The *dl* form of substance **2** was hydrogenated (after Raney nickel treatment) over 10% palladium-on-carbon to give *dl*-5β-pregnan-20-one, mp 112–113.5°, after crystallization from ethanol (*Anal.* Found: C, 83.5; H, 11.1). The *d* form of **2**, on hydrogenation as above, gave the known[5] *d*-5β-pregnan-20-one. Three recrystallizations from methanol gave colorless needles, mp 114.5–115.5° ($[\alpha]D$ +111°[4]), undepressed on admixture with authentic, naturally derived material, mp 113–115.5°.[6] The ir spectra (KBr) of the two samples were identical.

The optical purities of the cyclization products were determined as follows. A sample of *d*-**2**, $[\alpha]D$ +169°,[4] was hydrogenated as above and the product was chromatographed on Florisil. The rotation of the total dihydro-**2** fraction was $[\alpha]D$ +105°,[4] corresponding to an optical purity of 95.5%. Thus the rotation of

(1) R. L. Markezich, W. E. Willy, B. E. McCarry, and W. S. Johnson, *J. Amer. Chem. Soc.*, **95**, 4414 (1973).
(2) W. S. Johnson, M. B. Gravestock, and B. E. McCarry, *ibid.*, **93**, 4332 (1971).
(3) The nmr spectrum at 60 MHz ($CDCl_3$ solvent and TMS internal standard) as well as the ir spectrum were entirely consistent with the assigned structure.
(4) Rotations were recorded at 22° using dilute (0.003–0.08 *M*) solutions in chloroform in a 1-dm tube.
(5) Reported for naturally derived 5β-pregnan-20-one, mp 114–115°, $[\alpha]^{16-22}D$ +110° ($CHCl_3$): L. Gyermek, J. Iriarte, and P. Crabbé, *J. Med. Chem.*, **11**, 117 (1968).
(6) We wish to thank Dr. J. A. Edwards of Syntex for providing us with this specimen.

optically pure *d*-**2** is calculated to be $[\alpha]D$ +177°. Cyclization of a sample of *d*-**1** derived from *d*-trienynone[1] having $[\alpha]D$ +58.4°[4] yielded a specimen of *d*-**2** which, after chromatography to remove only the 17α epimer, gave a rotation of $[\alpha]D$ +161°[4] corresponding to an optical purity of 91%. Similarly *l*-**1** derived from **1**-trienynone,[1] $[\alpha]D$ −58.0°,[4] afforded *l*-**2**, $[\alpha]D$ −163° (92% optical purity).

There are a number of variations, involving conventional reactions, that can be envisaged for the transformation of the substance *d*-**2** into useful steroids. We have given preliminary attention to two pathways, which lead to progesterone, but yields have not been optimized. Thus, oxidation of *d*-**2** with *tert*-butyl chromate[7] afforded the enedione **3** (yield *ca.* 60%), which, without purification, was selectively hydrogenated over palladium-on-carbon to give 5β-pregnane-3,20-dione (**4**). Chromatography over Florisil followed by repeated recrystallizations from hexane afforded a pure specimen of the 17β epimer, mp 118.5–120°, undepressed on admixture with authentic, naturally derived 5β-pregnane-3,20-dione,[8] mp 119–120.5°. The ir spectra (KBr) of the two specimens were identical. The conversion of this substance (by bromination followed by dehydrobromination) into progesterone is already known.[8]

An alternative and shorter approach to progesterone which was examined only in the *dl* series consisted of dehydrogenation of *dl*-**3** with dichlorodicyanoquinone[9] to give the dienedione **6**[3] (88% yield by vpc), mp 175–176° after recrystallization from ethyl acetate–hexane (*Anal.* Found: C, 80.7; H, 8.7). Selective hydrogenation of this product in the presence of tris(triphenylphosphine)rhodium(I) iodide[10] gave, after preparative tlc and recrystallization from methanol, *dl*-progesterone. The nmr and solution ir spectra of this sample were identical with the corresponding spectra of naturally derived progesterone as well as of authentic *dl*-progesterone.[2]

Acknowledgment. We are indebted to the National Institutes of Health and the National Science Foundation for support of this research.

(7) L. F. Fieser and M. Fieser, "Reagents for Organic Synthesis," Vol. 1, Wiley, New York, N. Y., 1967, p 86.
(8) See *inter alia* F. Johnson, G. T. Newbold, and F. S. Spring, *J. Chem. Soc.*, 1302 (1954).
(9) *Cf.* A. B. Turner and H. J. Ringold, *J. Chem. Soc. C*, 1720 (1967).
(10) J. F. Young, J. A. Osborne, F. H. Jordine, and G. Wilkinson, *Chem. Commun.*, 131 (1965).

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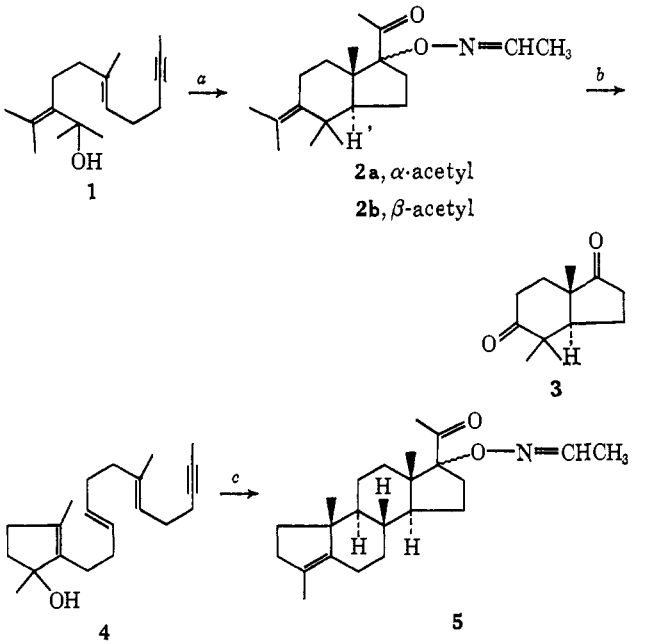
Acetylenic Bond Participation in Biogenetic-Like Olefinic Cyclizations in Nitroalkane Solvents.[1] Synthesis of the 17-Hydroxy-5β-pregnan-20-one System

Sir:

In previous[1-3] communications we have disclosed that allylic alcohols **1**, **4**, and **6** may be induced to undergo stereospecific cyclization to form bicyclic (from **1**) and tetracyclic (from **4** and **6**) products. In each case, an intermediary polycyclic vinyl cation is presumably formed, which is trapped by various nucleophiles (*e.g.*, formic acid, acetonitrile, and ethylene carbonate). In the present communication we report that these reactive vinyl cations may also be trapped by nitroalkanes to afford oxime ethers (*e.g.*, **2**, **5**, and **7**), and that these substances provide an entry into the 17-hydroxypregnan-20-one system.

The results of preliminary experiments are summarized in Scheme I. Treatment of a solution of the

Scheme I



[a] CF_3CO_2H, $CH_3CH_2NO_2$, N_2, −78°, 15 min. [b] RuO_4, CCl_4, 23°, 3 hr. [c] CF_3CO_2H, $(CH_3)_3N$, $CH_3CH_2NO_2$, N_2, −25°, 2 hr.

allylic alcohol **1**[2] in nitroethane at −78° with excess trifluoroacetic acid resulted in the formation of the isomeric oxime ethers **2** (*ca.* 80% yield of a 1:1 mixture of epimers, by vpc). A sample was purified by preparative tlc on silica gel (1:9 ethyl acetate–hexane); mass spectrum *m/e* 305 (M^+); λ_{max}^{film} 5.83 (C=O) and 6.12 (C=N) μ. The nmr spectrum[4] of a chromatography fraction enriched in **2a** included singlets at δ 1.07 (3 H) and 1.20 (6 H) for the three methyl groups attached to quaternary carbon atoms, and at 1.66 (3 H) and 1.80 (3 H) for the isopropylidene methyl groups. In addition, there was a singlet at δ 2.07 (3 H, acetyl methyl), a doublet (J = 6 Hz) at 1.90 (3 H, N=CHCH_3), and a quartet (J = 6 Hz) at 6.83 (1 H, N=CHCH$_3$). The nmr spectrum[4] of another chromatography fraction enriched in **2b** included three-proton singlets at δ 0.70, 1.15, 1.23, 1.70, and 1.82 (see above) in addition to a singlet at 2.03 (3 H, acetyl methyl), a doublet (J = 6

(1) For the previous papers in this series see (a) R. L. Markezich, W. E. Willy, B. E. McCarry, and W. S. Johnson, *J. Amer. Chem. Soc.*, **95**, 4414 (1973); (b) B. E. McCarry, R. L. Markezich, and W. S. Johnson, *ibid.*, **95**, 4416 (1973).
(2) W. S. Johnson, M. B. Gravestock, R. J. Parry, R. F. Myers, T. A. Bryson, and D. H. Miles, *ibid.*, **93**, 4330 (1971).
(3) W. S. Johnson, M. B. Gravestock, and B. E. McCarry, *ibid.*, **93**, 4332 (1971).
(4) The nmr spectrum at 60 MHz (TMS internal standard, $CDCl_3$ solvent) was entirely consistent with the assigned structure. Details are not recorded here, except for absorptions of particular significance.