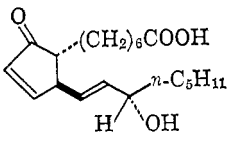
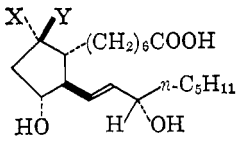
of conversion to prostaglandin B_1[1] [λ_{max} 278 nm (ϵ 28,600)] in 0.11 *N* methanolic potassium hydroxide identical with that for natural prostaglandin E_1; and (3) thin-layer chromatographic behavior on silica gel using several solvent systems identical with that of authentic E_1. The same comparative studies were also made with synthetic and natural samples of 15-epi-prostaglandin E_1, confirming the nature of this synthetic product.

Synthetic *dl*-prostaglandin E_1 was converted to *dl*-prostaglandin A_1 (**10**) using 0.5 *N* hydrochloric acid in 1:1 water–tetrahydrofuran (60 hr, 25°) and isolated by chromatography as a colorless oil, spectroscopically identical with natural prostaglandin A_1 and possessing one-half its biological activity. Reduction of synthetic **9** using sodium borohydride in methanol at 0° followed



10



11, X = OH; Y = H
12, X = H; Y = OH

by chromatographic isolation afforded *dl*-prostaglandin $F_{1\alpha}$ (**11**), mp 81°, and *dl*-prostaglandin $F_{1\beta}$ (**12**), mp 116.4–116.8°, spectroscopically and chromatographically identical, respectively, with natural[14] prostaglandin $F_{1\alpha}$ and $F_{1\beta}$.

Further studies on the synthesis of prostaglandins by this and other routes are under way. We shall report on the control of stereochemistry at C_{15} and on the resolution of our synthetic prostaglandins in due course.

Acknowledgment. This work was generously supported by the National Institutes of Health. We are grateful to Professor Sune Bergström for first arousing our interest in the prostaglandins during a visit by one of us to his laboratory at Lund in 1957. Finally, we are pleased to acknowledge help in various aspects of the problem from Drs. Tse Lok Ho, Manning Cooke, Jr., and Kenn Harding.

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Robert M. Carlson, Joachim Paust
Edwin Vedejs, Isidoros Vlattas, Rudolph E. K. Winter
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Received April 15, 1968

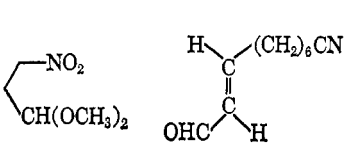
A New Total Synthesis of Prostaglandins of the E_1 and F_1 Series Including 11-Epiprostaglandins

Sir:

A previous communication[1] describes the total synthesis of *dl*-prostaglandins E_1, $F_{1\alpha}$, $F_{1\beta}$, A_1, and B_1. We report herein a second and different synthetic route to these substances which can be adapted to provide the C_{11} epimers of the natural E_1 and F_1 hormones as well as either of the corresponding C_{15} epimers.[1] Of special note in this connection is the discovery that certain of these synthetic stereoisomers of prostaglandin E_1 manifest interesting, potent, and possibly useful biological activity.

(1) E. J. Corey, N. H. Andersen, R. M. Carlson, J. Paust, E. Vedejs, I. Vlattas, and R. E. K. Winter, *J. Am. Chem. Soc.*, **90**, 3245 (1968).

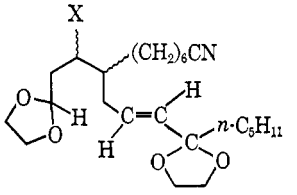
Reaction of 3-nitropropanal dimethyl acetal (**1**)[2,3] with 9-cyano-2-nonenal (**2**)[3,4] in the presence of base led to the Michael adduct **3**,[3,5] which was converted to the conjugated enone **4**[3,5] (80%) by reaction[6] with the sodio derivative of dimethyl 2-oxoheptylphosphonate;[7] molecular ion of **4** at *m/e* 410.2781 (theory 410.2773).[8] Reaction of **4** with ethylene glycol–*p*-toluenesulfonic



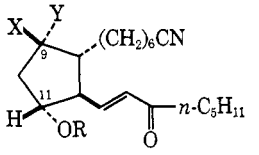
1 **2**

3, X = O
4, X = CHCO–*n*-C_5H_{11}

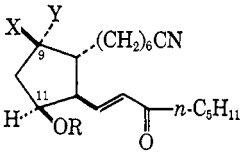
acid in benzene produced the nitro bisdioxolane **5**[3,5] (89%), molecular ion at *m/e* 452.2880 (theory 452.2886), which gave after reduction [(Al–Hg)–Et_2O–H_2O–CH_3OH][1] and formylation (formic acetic anhydride) the corresponding formylamino bisdioxolane **6**,[3] molecular ion at *m/e* 450.3089 (theory 450.3094) (*Anal.* Found: C, 66.52; H, 9.61; N, 6.22). Treatment of the bis-



5, X = NO_2
6, X = NHCHO



7a, X = HCONH; Y = H
b, X = H; Y = HCONH



8a, X = HCONH; Y = H
b, X = H; Y = HCONH

dioxolane **6** with *p*-toluenesulfonic acid in acetone at 25° for 40 hr led to four stereoisomeric cyclization products in 85% total yield; these were cleanly separated by chromatography (silica gel; $CHCl_3$–Et_2O–CH_3OH, 5:4.5:0.5) into the pairs of alcohols **7a** + **8b** (R = H), R_f 0.12 and **7b** + **8a** (R = H), R_f 0.20. The latter pair was separated cleanly by chromatography on neutral alumina using the same solvent system to give pure **7b** (R = H), R_f 0.45,[3,5] and **8a** (R = H), R_f

(2) Prepared from 3-bromopropanal dimethyl acetal and sodium nitrite in dimethyl sulfoxide; bp 96° (15 mm) (*Anal.* Found: C, 40.33; H, 7.54; N, 9.19); see N. Kornblum, H. O. Larson, R. K. Blackwood, D. D. Mooberry, E. P. Oliveto, and G. E. Graham, *ibid.*, **78**, 1497 (1956).

(3) The infrared and nuclear magnetic resonance spectra of this substance were in excellent agreement with the assigned structure.

(4) Prepared from 7-cyanoheptanal[1] and formylmethylenetriphenylphosphorane and purified by evaporative distillation *in vacuo* (*Anal.* Found: C, 72.52; H, 9.08; N, 8.37).

(5) This liquid substance was not sufficiently stable to allow distillation at 1 μ; however, isolation in sufficiently pure form (>95%) for further transformations was readily effected chromatographically.

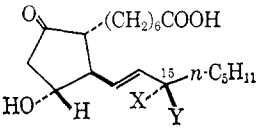
(6) (a) W. S. Wadsworth and W. D. Emmons, *J. Am. Chem. Soc.*, **83**, 1733 (1961); (b) L. Horner, H. Hoffmann, W. Klink, H. Ertel, and V. G. Toscano, *Ber.*, **95**, 581 (1962), and earlier papers.

(7) Prepared from ethyl hexanoate and dimethyl α-lithiomethanephosphonate: E. J. Corey and G. T. Kwiatkowski, *J. Am. Chem. Soc.*, **88**, 5654 (1966).

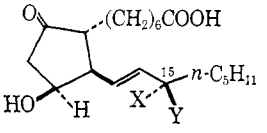
(8) High-resolution mass spectral determinations were performed with an AEI-MS-9 double-focusing spectrometer.

0.55.[3,5] The former pair was resolved chromatographically (silica gel; $CHCl_3$–Et_2O–CH_3OH, 5:5:0.1) after acetylation to afford the acetates **7a** (R = CH_3CO),[3] mp 56.5°, R_f 0.26, and **8b** (R = CH_3CO),[3,5] R_f 0.15. The formulation of the crystalline acetate, mp 56.5°, as **7a** follows from its identity (melting point, mixture melting point, spectroscopic) with the substance of this structure which was obtained as an intermediate in the previously described synthesis[1] of *dl*-prostaglandin E_1 (**9a**) and from its actual conversion[1] to *dl*-prostaglandin E_1.

The oily stereoisomers[9] **7b**, **8a**, and **8b** were separately transformed to prostaglandins in the E_1 series by the sequence previously described[1] with the result that **7b** produced pure *dl*-prostaglandin E_1 (**9a**) and pure *dl*-15-epiprostaglandin E_1 (**9b**) (readily separated chromatographically), and **8a** and **8b** each produced *dl*-11-epiprostaglandin E_1 (**10a**),[3] mp 92.5–93°, and *dl*-11,15-epiprostaglandin E_1 (**10b**),[3] mp 88.6–89.3°. The 11-epi formulations **10a,b** were verified by acid-catalyzed elimination of water to form, respectively, *dl*-prostaglandin A_1 and *dl*-15-epiprostaglandin A_1. Satisfactory analytical data were obtained for **10a** (*Anal.* Found: C, 67.84; H, 9.71) and for **10b** (*Anal.* Found: C, 67.54; H, 9.76).



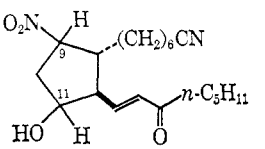
9a, X = OH; Y = H
b, X = H; Y = OH



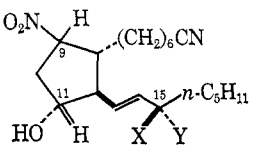
10a, X = OH; Y = H
b, X = H; Y = OH

The cyclization of **6** by the procedure described above led to C_{11}-normal and C_{11}-epi products in approximately equal amount. However, the ratio of these products depends on the conditions employed for cyclization, and, for example, use of 4% sulfuric acid in 1:1 tetrahydrofuran–water at 25° for 24 hr resulted in the formation of twice as much C_{11}-epi as C_{11}-normal cyclization product.

The synthesis of prostaglandins by direct acid-catalyzed cyclization of the nitro ketal **5** has also been accomplished. Thus, treatment of **5** with trifluoroacetic acid containing some triethylamine (initially at −10 to 25° over 1 hr and at 25° for 5 hr) followed by brief (20 sec) exposure to methanolic base at 0° produced a mixture of four stereoisomers of structure **11** which was easily separated by column chromatography on silica gel ($CHCl_3$ eluent) into a less mobile pair of C_{11}-normal alcohols epimeric at C_9 and a more mobile pair of C_{11}-epi alcohols epimeric at C_9. Reduction of the carbonyl function ($NaBH_4$) of the former pair of C_9 epimers



11



12, X = H; Y = OH
13, X = OH; Y = H

(C_{11} normal) led to a mixture of alcohols which was easily separated by chromatography on silica gel into a (less mobile) pair of C_{15}-normal alcohols epimeric at C_9 (**12**) and a (more mobile) pair of C_{15}-epi alcohols epimeric at C_9 (**13**). The pair **12** was converted to *dl*-prostaglandin E_1 by the previously described sequence[1] and, analogously, the pair **13** gave *dl*-15-epiprostaglandin E_1. Similarly, the 9-epimeric pair of nitro alcohols **11** in the C_{11}-epi series was converted after reduction and separation of C_{15} epimers into racemic C_{11}-epi- and 11,15-epiprostaglandin E_1. It is important to note that, with a nitro substituent at C_9, facile chromatographic separation of intermediates according to configuration at C_{11} and also C_{15} is possible. In addition, it has been found that 2,3-dicyano-5,6-dichloro-*p*-benzoquinone effects the selective oxidation of the Δ^{13}-15-hydroxy unit to the Δ^{13}-15-ketone unit in high yield, thus making it possible by the use of recycling of one of the isomeric C_{15} alcohols to direct the synthesis toward either C_{15}-normal or C_{15}-epi prostaglandins. Finally, since asymmetry at C_9 is removed in the later stages of synthesis, the occurrence of mixtures of C_9 epimers in this route is relatively unimportant.

Research is continuing on other modifications of the general synthetic approach to prostaglandins described herein, one objective being the complete control of stereochemistry, especially at C_{11}. A number of distinctly different synthetic routes to prostaglandins are also under study.

The racemic 11, 15, and 11,15 epimers of prostaglandin E_1 are all highly active biologically.[10] Of especial interest is the finding that *dl*-11,15-epiprostaglandin E_1 is about twice as active as *dl*-prostaglandin E_1 in tests on smooth muscle from rat uterus, but much less active in tests of vasodepression (in rats).

Acknowledgment. This work was generously supported by the National Institutes of Health.

(9) (a) For acetates **7a** and **8b** (R = CH_3CO), the molecular ions were found to have *m/e* 404.2687 and 404.2683, respectively (theory 404.2675); (b) for alcohols **7b** and **8a** (R = H), the molecular ions were found to have *m/e* 362.2564 and 362.2571, respectively (theory 362.2569).

(10) We are indebted to Drs. Peter Ramwell and Jane Shaw of the Worcester Foundation for Experimental Biology for quantitative biological measurements, the results of which will be published in full at a later time.

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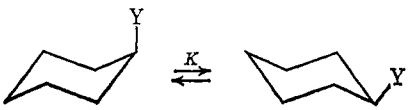
The Conformational Preferences of Cyclohexyl Grignard Reagents

Sir:

Probably the simplest measure of steric interactions is the difference in free-energy content of axial and equatorial cyclohexane derivatives, which, expressed in kilocalories/mole, has been defined as the *A* value[1] and



(1)

equals $-\Delta F = RT \ln K$.[2] It has been shown that these preferences are not simply related to the size

(1) S. Winstein and H. J. Holness, *J. Am. Chem. Soc.*, 77, 5562 (1955).
(2) E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison, "Conformational Analysis," Interscience Publishers, Inc., New York, N. Y., 1965, p 129.