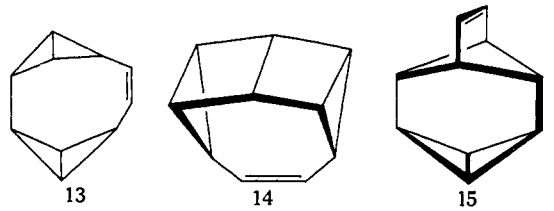
in terms of polygonal[16a] and nonpolygonal graphs[16b] revealed that unknown hydrocarbons **12–15** were the only remaining feasible structural representations



13 14 15

(other than **11** and **12**). Of this group, **13** and **14** are incompatible with the nmr data, and **15** is discounted for mechanistic reasons.

Investigations of these and new types of metal ion induced isomerizations will continue to be made. Also, examination of the ground- and excited-state properties of **5**, **6**, **7**, and **11** is presently in progress.

Acknowledgment. We wish to thank Badische Anilin- und Soda-Fabrik for a generous gift of cyclooctatetraene required in the preparations of **1**, **4**, and **8**.

(16) (a) Those molecules in which a continuous cycle of 10 atoms may be found; (b) those molecules which contain no continuous cycle of 10 atoms.

(17) National Institutes of Health Postdoctoral Fellow, 1969–1970.

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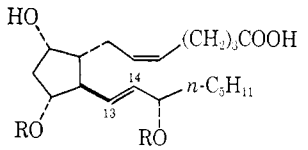
Total Synthesis of Prostaglandins $F_{1\alpha}$, E_1, $F_{2\alpha}$, and E_2 (Natural Forms) from a Common Synthetic Intermediate

Sir:

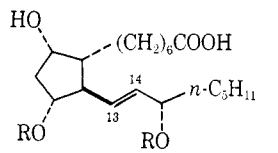
An effective stereocontrolled total synthesis of the naturally occurring hormones prostaglandins $F_{2\alpha}$ and E_2 has been reported recently from these laboratories.[1,2] These substances are produced from a common synthetic intermediate, the (dextrorotatory) 11,15-bistetrahydropyranyl ether of prostaglandin $F_{2\alpha}$ (**1**).[1] The intermediate **1** has now been employed successfully in the synthesis of the prostaglandins of the first series,[3] including the primary prostaglandins $F_{1\alpha}$ and E_1.

Hydrogenation of a solution of **1** ($[\alpha]^{24}D$ +13.3°, *c* 1.0 in chloroform) was carried out in methanol as solvent at −15 to −20° under 1 atm of hydrogen with 5% palladium-on-carbon (Engelhard Industries, Inc.) (amount, 0.25 times weight of substrate **1**) as catalyst using a thin layer chromatographic (tlc) analytical technique to follow the progress of reaction. The hydrogenation was interrupted as soon as tlc analysis[4] indicated that the only reaction components were the 11,15-bistetrahydropyranyl ether of prostaglandin $F_{1\alpha}$ (major product) (**2**) and its 13,14-dihydro derivative (in small amount).[5] The average time required for hydrogenation to this point was *ca.* 3 hr. The reaction product was isolated and subjected to hydrolysis in acetic acid–water–tetrahydrofuran (20:10:3) at 40° for 4 hr. Reisolation and chromatographic purification on silica gel (benzene–tetrahydrofuran–formic acid, 15:5:2, as eluent) afforded in 80% yield prostaglandin $F_{1\alpha}$ as a crystalline solid which was chromatographically homogeneous. Recrystallization from ethyl acetate–cyclohexane afforded fine colorless needles of prostaglandin $F_{1\alpha}$ (**3**), mp and mmp (with a sample of natural **3**) 101.5–102.5°, $[\alpha]^{24}D$ +24° (*c* 0.87, tetrahydrofuran). The infrared and nmr spectra and chromatographic behavior of synthetic and natural samples of prostaglandin $F_{1\alpha}$ were identical.

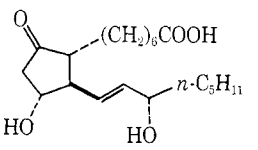
Oxidation of a sample of **2** obtained as described above with Jones chromic acid reagent[1] at −10° for 5 min and subsequent work-up and hydrolysis in acetic acid–water–tetrahydrofuran (20:10:3) at 39° for 7 hr afforded a product which was chromatographed on acid-washed silica gel using acetone–ethyl acetate–cyclohexane (1:2:2) as eluent and recrystallized from ethyl acetate–cyclohexane to give prostaglandin E_1 (**4**) (63.5% from **1**), mp and mmp 113.5–114.0°, $[\alpha]^{26}D$ −61.1° (*c* 0.256, tetrahydrofuran).[6] The spectra and chromatographic properties of synthetic and natural samples of prostaglandin E_1 were identical.



1, R = tetrahydropyranyl



2, R = tetrahydropyranyl
3, R = H



4

The reduction method described above has also been applied to the synthesis of tritium-labeled prostaglandins of high specific activity, including prostaglandin $F_{1\alpha}$ (from **1**) and prostaglandin E_1 (from the corresponding 11,15-bistetrahydropyranyl ether). The labeled prostaglandins, obtained using carrier-free tritium gas with isopropyl alcohol as the solvent for hydrogenation, are now commercially available (New England Nuclear Co.).

This work completes a second total synthesis of the E_1 and $F_{1\alpha}$ prostaglandins in natural optically active

(1) E. J. Corey, T. K. Schaaf, W. Huber, U. Koelliker, and N. M. Weinshenker, *J. Amer. Chem. Soc.*, **92**, 397 (1970).

(2) See also E. J. Corey, N. M. Weinshenker, T. K. Schaaf, and W. Huber, *ibid.*, **91**, 5675 (1969).

(3) See S. Bergström, *Science*, **157**, 382 (1967).

(4) Aliquots of the reaction mixture were subjected to hydrolysis in 1:1 methanol–0.1 *N* hydrochloric acid at 75° for 2 min to remove the tetrahydropyranyl groups and analyzed by tlc using silver nitrate impregnated silica gel plates with the ethyl acetate–acetic acid–methanol–2,2,4-trimethylpentane–water (110:30:35:10:100) system as eluent [see K. Gréen and B. Samuelsson, *J. Lipid Res.*, **5**, 117 (1964)]. For this tlc system the R_f values for prostaglandin $F_{2\alpha}$, prostaglandin $F_{1\alpha}$, 13,14-dihydroprostaglandin $F_{2\alpha}$, and 13,14-dihydroprostaglandin $F_{1\alpha}$ were found to be 0.47, 0.64, 0.57, and 0.74, respectively.

(5) If the hydrogenation is stopped immediately after consumption of the starting material, the reaction mixture is found to contain in addition to the major component **2** small amounts of the bistetrahydropyranyl ethers of 13,14-dihydroprostaglandin $F_{2\alpha}$ and 13,14-dihydroprostaglandin $F_{1\alpha}$. Because 13,14-dihydroprostaglandin $F_{2\alpha}$ is much less readily separated by chromatography from prostaglandin $F_{1\alpha}$ than is 13,14-dihydroprostaglandin $F_{1\alpha}$, it is advantageous to carry out hydrogenation until 13,14-dihydroprostaglandin $F_{2\alpha}$ has been saturated. Chromatographic separation of the various bistetrahydropyranyl ethers is quite difficult, and for this reason the THP protecting group is removed for analysis or purification on a preparative scale.

(6) Reported previously for prostaglandin E_1, $[\alpha]^{25}D$ −61.6°; see E. J. Corey, I. Vlattas, and K. Harding, *J. Amer. Chem. Soc.*, **91**, 535 (1969).

form (for the previous synthesis see ref 6 and earlier papers therein cited). The transformations reported herein also mark the realization of the synthesis of the four primary prostaglandins, $F_{1\alpha}$, E_1, $F_{2\alpha}$, and E_2, from a single precursor, the intermediate **1**, a point of major practical importance.[7]

(7) This work was assisted financially by a grant from the National Institutes of Health.

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Calorimetric Determination of Heats of Formation of Hydrogen Bonds

Sir:

We wish to report the results of an investigation designed to test the reliability of heats of formation of hydrogen bonds determined by one of the calorimetric methods that have been devised in recent years.[1-3] While there are important differences in the thoroughness of the different techniques and in the reliability of the results obtained, the reported values refer to one of the two processes

$$A(I) + B(I) \longrightarrow AB(I) \quad (1)$$

or

$$A(I) + B(B) + M(B) \longrightarrow AB(B) + M(I) \quad (2)$$

In processes 1 and 2, the symbols A, B, AB, and I refer to the acid, the base, the hydrogen-bonded complex, and an inert solvent, respectively. The symbol M represents a "model" compound, which hopefully accounts for solvent–solute interactions other than hydrogen bonds between the acid and the solvents.[3] Parentheses indicate that the preceding species is extremely dilute in the indicated solvent. The methods of Drago[1] and Lamberts[2] and Arnett's Method I[3] may be represented by process 1; Arnett's Method II[3] by process 2. Arnett has shown that the two methods give essentially the same results for hydrogen bonds between phenol and several bases with carbon tetrachloride as inert solvent. Drago and Epley[4] have studied several acid–base pairs in different inert solvents, cyclohexane and carbon tetrachloride, and found that the results may be quite different. While we feel that their heats in cyclohexane are much less reliable than reported, as will be indicated later, the discrepancy between the heats of hydrogen bonding in the two solvents is probably real.

Studies of a hydrogen bond in different solvents and by the two methods can provide useful information regarding interactions in solution, providing the reliability limits of the methods can be established. It is apparent that no single study by either method could detect the existence of strong interactions between the "inert" solvent and either the acid or the base. A comparison of the values determined by the two methods using the same "inert" solvent should detect such interactions between the solvent and the base, since in process 2 the two are never in contact. However, in the case of pyridine as base in carbon tetrachloride, where both Drago[4] and Lamberts[5] have suggested that such interactions exist, no discrepancy was noted between the values obtained by the two methods.[3] This comparison could not possibly detect interactions between the acid and the solvent, since the species A(I) is common to both methods.

As a first step in establishing these reliability limits, we have investigated the effects of different inert solvents and model compounds on the heats calculated for process 2. The inert solvents are carbon tetrachloride, cyclohexane, and *n*-heptane; the model compounds involve the substitution of a methoxy group (M_1) or a methyl group (M_2) for the hydroxy group of the parent acid. The heats of solution of phenol and its model compounds, anisole and toluene, were determined in the three inert solvents and the basic solvents pyridine, tetrahydrofuran (THF), *p*-dioxane, and acetone. The calorimeter has been described elsewhere[6] and experimental details will be given in a forthcoming paper.[7] All of the heats of solution in basic solvents and those for the model compounds in inert solvents are relatively independent of concentration. The heat of solution of phenol in the hydrocarbon solvents is strongly dependent on composition ($\Delta H = 7.625 - 8.0\ m \pm 0.02$ kcal mol^{-1} between 0.004 and 0.03 *m* in cyclohexane). This concentration dependence, which is probably due to self-association of phenol, was not noted by Epley and Drago[8] in their determinations of heats of hydrogen bonding in this solvent at even greater concentrations of phenol. Since the assumption of an ideal dilute solution is inherent in the treatment of data with process 1, the reliability limits on heats of formation of hydrogen bonds in this solvent must be regarded as questionable.

Our heats of solution, extrapolated to infinite dilution, were combined to give the heats for process 2 listed in Table I, along with values that have been reported for process 1. These heats indicate that the heats of formation of hydrogen bonds determined by this method are strongly dependent on the choice of both the inert solvent and the model compound. Since there is apparently no basis for choosing one model compound as more appropriate than the other, there is no guarantee that the actual heat of formation of the hydrogen bond lies within the range of the values calculated for different combinations of inert solvent and model compound. The values determined with carbon tetrachloride as inert solvent are significantly lower (0.2–0.9 kcal) than corresponding values in the hydrocarbon solvents, which could indicate relatively strong interactions of the former solvent with phenol.

In calculating the heats for process 2, we realized that the disparities between the model compounds apparently arise in their heats of solution in the inert

(1) T. F. Bolles and R. S. Drago, *J. Amer. Chem. Soc.*, **87**, 5015 (1965).
(2) L. Lamberts, *J. Chim. Phys.*, **62**, 1404 (1965).
(3) E. M. Arnett, T. S. S. R. Murty, P. von R. Schleyer, and L. Joris, *J. Amer. Chem. Soc.*, **89**, 5955 (1967).
(4) R. S. Drago and T. D. Epley, *ibid.*, **91**, 2883 (1969).
(5) D. Neerinck and L. Lamberts, *Bull. Soc. Chim. Belges*, **75**, 473 (1966).
(6) G. L. Bertrand, R. D. Beaty, and H. A. Burns, *J. Chem. Eng. Data*, **13**, 436 (1968).
(7) In this paper, we will show that the heat determined for process 2 should refer to the heat of formation of the hydrogen bond with all species (A, B, and AB) at infinite dilution in pure base, assuming the acid is almost completely complexed.
(8) T. D. Epley and R. S. Drago, *J. Amer. Chem. Soc.*, **89**, 5770 (1967).