8α-H). The A-60 nmr spectrum of 8-iso-PGE_1 (in acetone-d_6) is clearly different from that of PGE_1, especially in the 13,14 vinyl proton absorption pattern at δ 5.2–5.78 and in the chemical shifts of the 8 and 12 protons.[9]

Treatment of 8-iso-PGE_1 with potassium acetate in ethanol at room temperature for 110 hr gave a major product with the same thin layer chromatographic properties as PGE_1. Isolation and crystallization gave a 70% yield of material with the same melting point (114–115.5°) and mixture melting point as PGE_1. A 100-Mc nmr spectrum of this substance was identical with that of PGE_1.

The origin of this material has been investigated. Bioconversions using 8,11,14-eicosatrienoic-1-^{14}C acid as substrate showed that the yield of 8-iso-PGE_1 was less than 5% of that of PGE_1. Further, bioconversions to which PGE_1-^3H has been added gave 8-iso-PGE_1 which contained more than 1% of the added tritium. Treatment of PGE_1 with potassium acetate in ethanol at 25° for 100 hr gave pure 8-iso-PGE_1 after isolation and recrystallization; the ratio of 8-iso-PGE_1 to recovered PGE_1 was 1:9. Isomerization under the same condition of PGE_1-^3H (100 hr) and 8-iso-PGE_1-^3H (300 hr) has confirmed that at least 10% 8-iso-PGE_1 is present at equilibrium. We conclude that 8-iso-PGE_1 arises by isomerization of PGE_1; whether this equilibrium is established under physiological conditions remains to be determined.

Acknowledgment. We thank Dr. M. F. Grostic for running the mass spectra (Atlas CH-4) and Dr. W. A. Struck and his associates for the other analytical data.

(9) A manuscript describing a complete analysis of the 100-Mc nmr spectra of PGE_1 and 8-iso-PGE_1 is in preparation (Dr. G. Slomp, private communication).

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The Total Synthesis of Prostaglandins

Sir:

The total synthesis of amorphous *dl*-prostaglandin $F_1\alpha$ ($PGF_1\alpha$) and *dl*-prostaglandin E_1 (PGE_1) in impure form has been reported in a preliminary communication by Just and Simonovitch.[1] A more recent communication[2] by another group has stated that no detectable amounts of PGE_1 or $PGF_1\alpha$ were found on repetition of this route or various modifications of it. We wish to report our findings in this area which constitute a synthesis of crystalline *dl*-PGE_1 and *dl*-8-iso-PGE_1, involving solvolysis of bismesylates. Additionally, we have shown that intermediates described by Just and Simonovitch do produce, under modified conditions, *dl*-$PGF_1\alpha$ and *dl*-$PGF_1\beta$ methyl esters.[3]

(1) G. Just and C. Simonovitch, *Tetrahedron Letters*, 2093 (1967).
(2) K. G. Holden, B. Hwang, K. R. Williams, J. Weinstock, M. Harman, and J. A. Weisbach, *ibid.*, 1569 (1968).
(3) The "epoxide" route to 9-hydroxyprostaglandins (PGF-types) was studied collaboratively at McGill University and at The Upjohn Co. A full account of a detailed study of the experiments described in ref 1 is in preparation (authored jointly by the McGill and Upjohn groups).

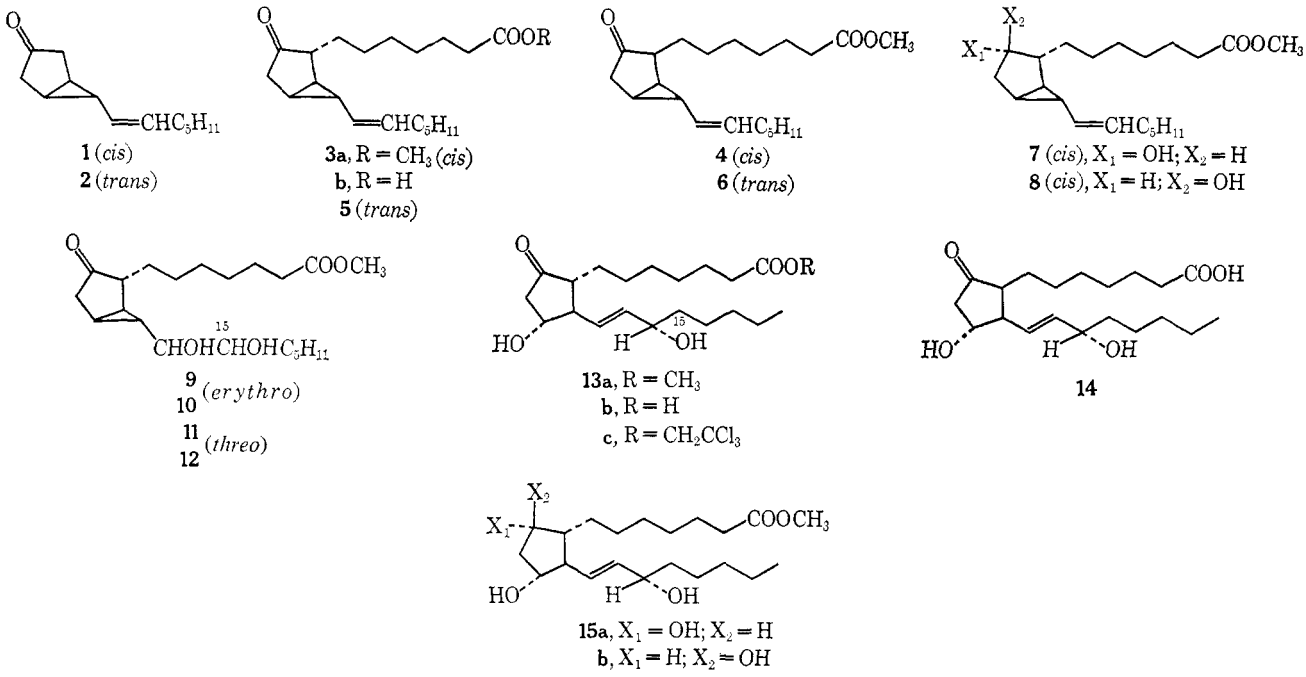
The *cis* and *trans* isomers of 6-*exo*-(1-heptenyl)-bicyclo[3.1.0]hexan-3-one[1] (**1** and **2**) were separated on a silver nitrate impregnated silica gel column, the *trans* form being eluted with 15% ethyl acetate in Skellysolve B, the *cis* with 25% ethyl acetate. The *cis* isomer **1** on alkylation with methyl ω-iodoheptanoate gave two isomeric keto esters, **3a** and **4**; the *trans* gave, analogously, **5** and **6**. Each pair was separated by silica gel chromatography (elution with ethyl acetate–Skellysolve B mixtures) and configurations of the C_7 side chains were assigned on the basis of the nmr spectra of their borohydride reduction products (see below). Base-catalyzed equilibration of pure **3a** and **4** gave the same rato of 35:65 (**3a**:**4**), showing the thermodynamic preference for the β-alkylated isomer **4**.

Sodium borohydride reduction in isopropyl alcohol at 0° of the α-alkylated isomer **3a** gave alcohols **7** and **8** in the ratio 1:9, while similar reduction of **4** gave the corresponding β-alkylated isomers in nearly equal amounts. The stereochemistry of these alcohols was assigned on the basis of their nmr spectra[4] and polarity on adsorbents and was confirmed by their further transformations to the 9α- and 9β-hydroxyprostaglandins of the "F" series and the corresponding 8-iso-PGF compounds.[3]

Hydroxylation of **3a** with osmium tetroxide gave two *erythro-vic*-glycol racemates **9** and **10**, while **5** gave the *threo* pairs **11** and **12**, each pair readily separable by silica gel chromatography. In contrast, the hydroxylation of **3a** and **5** with performic acid containing sodium formate[1] was quite nonstereospecific, giving all four possible *vic*-glycol racemates (70% total yield). Each of these four glycol racemates was converted to its bismethanesulfonate, which was solvolyzed in 2:1 acetone–water at 25°. From the solovolysis products was separated *dl*-prostaglandin E_1 methyl ester (**13a**; the yield varied from 5 to 10% depending on the starting glycol used), mp 55–57° (*Anal.* Found: C, 68.08; H, 9.92), along with similar amounts of *dl*-15-epi-PGE_1 methyl ester.[5] The major products in each case were unrearranged glycol 15-monomesylates resulting from hydrolysis of only the cyclopropylcarbinyl mesylate. The synthetic *dl*-PGE_1 methyl ester was characterized by identity of infrared, nmr, and mass spectra with those of natural material, by identical mobility and color reactions in several thin layer chromatographic systems, and by biological activity greater than 50% of natural material in two test systems.[6]

dl-PGE_1 (**13b**) was prepared by a modification of the above route. The mixture of alcohols **7** and **8**, obtained by reduction of **3a**, was hydrolyzed to the acids. These were reoxidized with chromic acid (Jones reagent at 0°) to the acid **3b**, which was hydroxylated with performic acid to a mixture of glycol acids analogous to the methyl esters **9**–**12**. These were esterified, using dicy-

(4) Relevant chemical shifts and couplings constants of **7** and **8** were very similar to those of thujyl and neothujyl alcohols; the β-alkylated isomers were related to those of isothujyl and neoisothujyl alcohols in the same way. See M. S. Bergqvist and T. Norin, *Arch. Kemi*, **22**, 137 (1964); K. Tori, *Chem. Pharm. Bull.* (Tokyo), **12**, 1439 (1964). Complete details of the nmr analysis will be published in our full paper.
(5) This was compared with (15*R*)-PGE_1 methyl ester prepared from natural (15*S*)-PGE_1 by epimerization of the allylic alcohol function in formic acid followed by esterification.
(6) Effects on smooth muscle (gerbil colon) and lowering of blood pressure in rats were measured in the laboratory of Dr. J. R. Weeks, Pharmacology Research, The Upjohn Co.



clohexylcarbodiimide, to the 2,2,2-trichloroethyl esters. Bismesylation and solvolysis of these glycol esters, without prior separation of isomers, gave *dl*-PGE_1 trichloroethyl ester (**13c**) in 4% yield. Removal of the trichloroethyl group by zinc in acetic acid[7] gave *dl*-PGE_1 (**13b**), mp 113.5–115°, in 70% yield. This is essentially the same melting point as the natural isomer, but the synthetic material showed no optical rotation between 475 and 230 mμ and the mixture melting point was slightly depressed. The fragmentation pattern of the mass spectrum was identical with that of natural PGE_1, and the synthetic material had about 60% of the biological activity of the natural isomer in two assays.[6] It showed the same tlc mobility and color reactions in several systems as natural PGE_1 and on treatment with base gave λ_{max} 278 mμ (ε 26,000).

The β-alkylated ketones **4** and **6** were also treated with osmium tetroxide to give four glycol racemates analogous to **9**–**12**, but with the β-oriented carboxyl side chain. Each of these gave, after mesylation and solvolysis, up to 10% yields of the *dl*-methyl ester of 8-iso-PGE_1 (**14**), mp 52–53° (*Anal.* Found: C, 67.80; H, 9.98). The nmr, ir, and mass spectra were identical with those of the methyl ester prepared from 8-iso-PGE_1 isolated from enzymatic conversions of bishomo-γ-linolenic acid using sheep seminal vesicles (the subject of a separate communication).[8]

dl-8-Iso-PGE_1, mp 101–102° (*Anal.* Found: C, 67.56; H, 9.60), was prepared from **4** *via* the same series of reactions as were used above for the preparation of *dl*-PGE_1 from **3** *via* trichloroethyl esters. The product showed nmr, ir, and mass spectra identical with those of authentic material[8] and their tlc mobilities were indistinguishable in several systems.

We have also found that epoxidation of **7** under mild conditions gave a mixture of isomeric epoxides. These, without separation, on treatment with formic acid at room temperature overnight followed by selective hydrolysis of formates, gave a complex mixture from which *dl*-prostaglandin $F_1\alpha$ methyl ester (**15a**), mp 70–73°, was isolated in 2–3% yield. Approximately the same amount of the 15 epimer[9] was also formed. In the same way, **8** was converted to epoxides which gave a 10% yield of *dl*-$PGF_1\beta$ methyl ester (**15b**), mp 101–102° (*Anal.* Found: C, 67.68; H, 10.71). Characterization of these products rests on the identity of infrared, nmr, and mass spectra with those of natural materials, identical mobility and color reactions in several thin layer chromatographic systems, and biological activity of at least 50% of the natural material in two systems.[6,10]

(7) R. B. Woodward, K. Heusler, J. Gosteli, P. Naegeli, W. Oppolzer, R. Ramage, S. Ranganathan, and H. Vorbrueggen, *J. Am. Chem. Soc.*, **88**, 852 (1966).

(8) E. G. Daniels, W. C. Kreuger, F. P. Kupiecki, J. E. Pike, and W. P. Schneider, *ibid.*, **90**, 5894 (1968).

(9) This was compared with a sample of (15*R*)-$PGF_1\beta$ methyl ester prepared from (15*S*)-$PGF_1\alpha$ as described in ref 5.

(10) We thank Dr. M. F. Grostic for the mass spectra, Dr. W. A. Struck and associates for other analytical data, and R. A. Morge, J. H. Kinner, and J. M. Baldwin for technical assistance.

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Is There Any Correlation between Quantum Yields and Triplet-State Reactivity in Type II Photoelimination?[1]

Sir:

We present some results which are particularly novel in that certain γ substituents which markedly increase the reactivity of phenyl ketones in type II photoelimination actually reduce the over-all quantum efficiency of the process, while others decrease triplet-state reactivity but increase quantum yields.

The various ketones listed in Table I were irradiated at 3131 Å as 0.10 *M* benzene solutions. Quantum yields of acetophenone formation (Φ_{II}) were determined by parallel irradiation of benzophenone–piperylene

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