NOTES

Preparation of [^{3}H]-Labelled prostaglandin E_1 by Hydrogenation of prostaglandin E_2 over $RhCl(PPH_3)_3$

An example of selectivity in homogeneous hydrogenation

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INTRODUCTION.

Labelled prostaglandin E_1 (PGE_1) (Fig. 1), which is used in biochemical and biological studies, can be prepared biosynthetically [1] from labelled dihomo-γ-linolenic acid or, particularly when high specific activities are required, by catalytic hydrogenation of prostaglandin E_2 (PGE_2) over a Pd-C-catalyst [2]. The latter method, however, gives a complex mixture from which we could obtain PGE_1 in only 10 % yield.

We have now found that homogeneous hydrogenation of PGE_2 with $RhCl(PPh_3)_3$-catalyt [3] leads to much better results (yields up to 50 %).

EXPERIMENTAL.

Labelled hydrogen gas was obtained by reaction of ^3H_2O with $LiAlH_4$ in a vacuum line and subsequently stored over reduced pulverized BTS-catalyst (ex Badische Anilin und Soda Fabrik) to remove traces of oxygen (see Fig. 2). Traps with molecular sieve 3A at −196° C were used for the transport of the gas. The time of contact of $^3H_2$ with the molecular sieve should be as short as possible, since the latter always contains slowly exchangeable hydrogen. Freshly prepared [4] $RhCl(PPh_3)_3$ was dissolved in a mixture of 2 ml benzene and 3 ml acetone in the presence of $^3H_2$-gas at atmospheric pressure and added to the pure substrate at room temperature. The hydrogenation reaction was stopped by freezing the reaction mixture and trapping the hydrogen gas with molecular sieve.

An aliquot was directly esterified with diazomethane and analysed by gas liquid chromatography (GLC) at 227° C on a column of 5 % QF_1 on Diatoport S, pretreated with hexamethyl-disilazane [5]. The rest of the mixture was worked up in the usual way [5] via thin-layer chromatography (TLC)

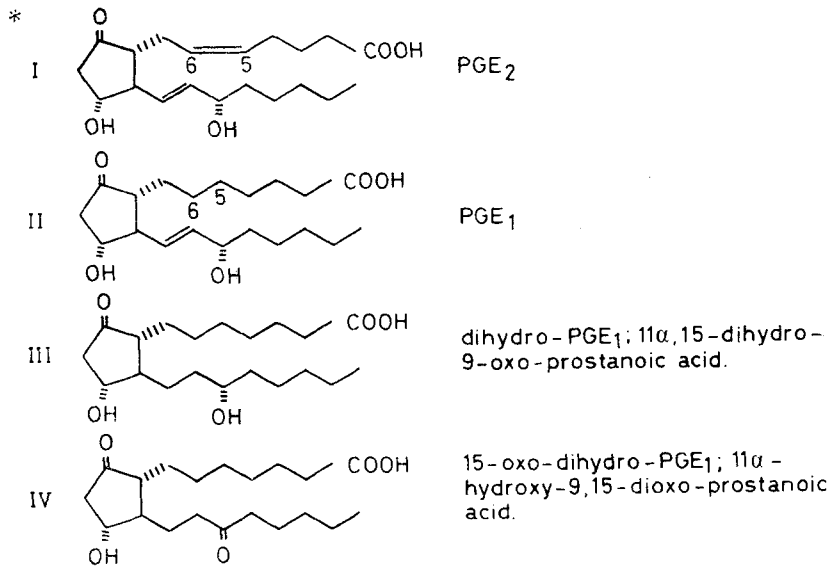

FIG. 1. Structural formulae of prostaglandin derivatives.

on 20 % $AgNO_3$-silicagel G plates, eluent $CHCl_3/CH_3OH/CH_3COOH/H_2O$ (95/7.5/1/0.6 v/v/v/v/). The plates were scanned with a Berthold thin-layer scanner for localization of the labelled products.

The amounts of PGE_1 and PGE_2 were determined by UV-spectrometry after alkali-conversion to PGB_1 and PGB_2 (ref. 6). Specific activities were determined by liquid scintillation counting in a Tricarb Model 3375.

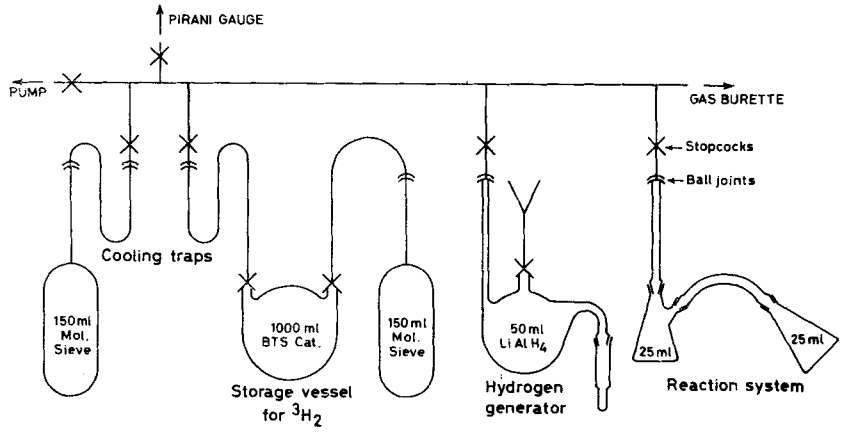

FIG. 2. Vacuum line for homogeneous catalytic hydrogenations with $^3H_2$.

RESULTS.

Apart from minor impurities, the reaction mixture consisted of 4 components with R_F values (TLC) of 0.6, 1, 1.3 and 1.7 ($PGE_1 = 1$) and retention times (GLC) of 0.9, 1, 1.1 and 1.3 ($PGE_1 = 1$), corresponding with PGE_2, PGE_1, dihydro-PGE_1 and, as appeared from infrared and mass spectroscopy, 15-oxo-dihydro-PGE_1 respectively. The latter product is probably formed from PGE_1, since PGE_1 itself also gives this product in a labelled form when $^3H_2$ is applied under the same reaction conditions as described above.

Overall yields of 30-50 % PGE_1 can be obtained (see Table 1). The results suggest that a reaction time of 5-6 h gives the highest yields. The amount of dihydro-PGE_1 appears to increase with time; the influence of time on the formation of 15-oxo-dihydro PGE_1 is less pronounced.

The table 1 shows that the recovery of labelled PGE_1 is better when more material is handled.

TABLE 1. Hydrogenation of PGE_2 with $RhCl(PPh_3)_3$.

PGE_2 (mg)	Catalyst (mg)	Reaction time (h)	Products* (%)				Overall yield of PGE_1 (%)
			I	II	III	IV	
1.5	1.1	20	4.5	24	24.5	47	11
1.8	5	20	—	51		49	32
1.5	5	5.5	3.5	70	6.5	20	34
1.5	5	1	33	35	—	32	23
15	5	17	6	19.5	29.5	45	20
15	5	6	3	72	5	20	52.5

* cf. Fig. 1.

DISCUSSION.

During homogeneous hydrogenation of isolated double bonds in the presence of $RhCl(PPh_3)_3$-catalyst isomerization does not occur [3,8–10]. We have checked this for tritiated stearate obtained from oleate. The stearate contained > 99 % of the ^3H at the 9- and 10-positions (for method of analysis see ref. 11). We assume therefore that PGE_1, labelled as described above, will contain ^3H only in the positions 5 and 6.

Our results indicate that the homogeneous catalytic hydrogenation of PGE_2 occurs with a remarkable selectivity, which cannot solely be ascribed to the preferential hydrogenation of cis double bonds [3,12].

In a recent study of 15-epi-PGA_2, Weinheimer and Spraggins [13], using palladium as catalyst, also found preferential hydrogenation occurring at the cis double bond at position 5, which is in agreement with our findings.

We have used the method described above for the synthesis of PGE_1 with a specific activity of 9.2 mCi/mmole, but higher specific activities are easily attainable.

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