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REACTION OF PENTA-*O*-BENZOYL-β-D-GLUCOPYRANOSE WITH TITANIUM TETRACHLORIDE AND PREPARATION OF COMPLEXES OF PERACYLATED, MIXED ESTERS OF GLUCOSE[*]

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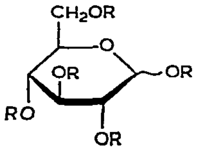
ABSTRACT

Preparative experiments and kinetic measurements have shown that penta-*O*-benzoyl-β-D-glucopyranose reacts instantaneously with titanium tetrachloride to give tetra-*O*-benzoyl-β-D-glucosyl chloride, which is anomerized to the α isomer by the catalytic action of benzoyloxytitanium trichloride, formed in the reaction as a by-product. Experiments with mixed acetic–benzoic esters indicate that complex formation, essential for the reaction to occur, takes place selectively, probably at the acyl group in position 1.

INTRODUCTION

It is known[1] that penta-*O*-benzoyl-β-D-glucopyranose (β-**1**) reacts with titanium tetrachloride in boiling chloroform solution to yield 2,3,4,6-tetra-*O*-benzoyl-α-D-glucopyranosyl chloride (α-**2**). One of the objects of the present work was to investigate whether the conversion proceeds by analogy with the reaction of penta-*O*-acetyl-β-D-glucopyranose (β-**3**) with $TiCl_4$, namely through the β-glycosyl halide intermediate (β-**2**). Further, by the preparation and investigation of penta-*O*-benzoyl- and tetra-*O*-acetyl-*O*-benzoyl-D-glucopyranose derivatives, we sought to elucidate



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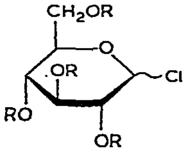
3 R = Ac



2 R = Bz
4 R = Ac

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[*] Dedicated to Professor Stephen J. Angyal on the occasion of his retirement.
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other details of the reaction mechanism leading to 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl chloride (α-**4**).

RESULTS AND DISCUSSION

In a special apparatus for formation of complexes[2], a 1 : 1 molar mixture of β-**1** and $TiCl_4$ was prepared in chloroform solution, and complex I (Table I) was precipitated from the solution by addition of petroleum ether. The composition of the complex is consistent with a 1 : 1 molar ratio and in acetonitrile solution it is moderately dextrorotatory. Decomposition of the complex with water gives a sugar derivative which, on the basis of its chlorine content, corresponds to **2**; thus the chlorination reaction takes place quantitatively in 5 min at room temperature.

It may be established from the i.r. spectrum of complex I (Fig. 1) that, in addition to the $\nu_{C=O}$ band of the free carbonyl groups (1730 cm^{-1}), there is also a $\nu_{C=O}$ band at 1630 cm^{-1} attributable to formation of the complex. Moreover, a new band is found at 1520 cm^{-1}.

In the next experiment, the petroleum ether needed for precipitation of the complex was added, together with titanium tetrachloride, to the solution of β-**1** in chloroform, and caused immediate separation of the resulting complex (complex II). The chlorine content of the product obtained upon aqueous decomposition indicates that, even under these conditions, chlorination occurs to the extent of ~80%.

TABLE I

$TiCl_4$ COMPLEXES OF BENZOYLATED D-GLUCOSES

No.		*Complex*				*Decomposition product*		
		Cl (%) *Found*	*Calc.*	Ti (%) *Found*	*Calc.*	$[\alpha]_D^{20}$ (CH_3CN)	Cl (%) *Found*	*Calc.*
I	β-**1**–$TiCl_4$, 1:1	15.83	15.91	5.62	5.38	+42.7°	5.69	5.78
II	β-**1**–$TiCl_4$, 1:1 in $CHCl_3$–petr. ether mixture	15.90	15.91	4.96	5.38	—	4.57	5.78
III	β-**1**–$TiCl_4$, 1:2	26.07	26.21	8.75	8.85	+39.0°	5.76	5.78
IV	α-**2**–$TiCl_4$, 1:1	21.46	22.00	6.38	5.96	+110.1°		
V	2,3,4,6-Tetra-*O*-acetyl-1-*O*-benzoyl-β-D-glucopyranose–$TiCl_4$, 1:1	22.48	22.10					
VI	2,3,4,6-Tetra-*O*-acetyl-1-*O*-benzoyl-α-D-glucopyranose–$TiCl_4$, 1:1	22.80	22.10					
VII	1,2,3,4-Tetra-*O*-acetyl-6-*O*-benzoyl-β-D-glucopyranose–$TiCl_4$, 1:1	22.30	22.10					

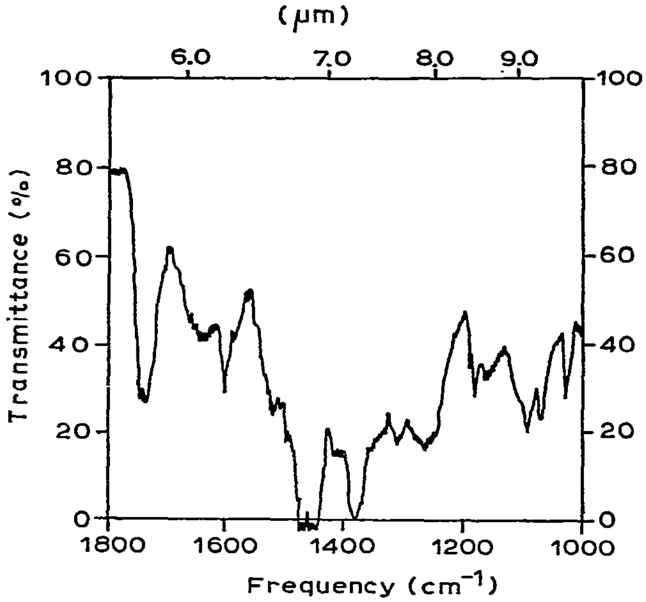

Fig. 1. I.r. spectrum of the 1:1 β-1–$TiCl_4$ complex.

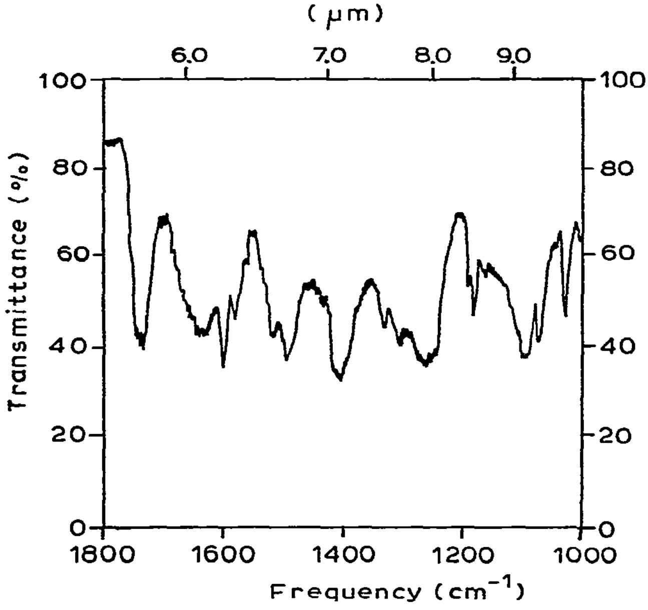

Fig. 2. I.r. spectrum of the 1:2 β-1–$TiCl_4$ complex.

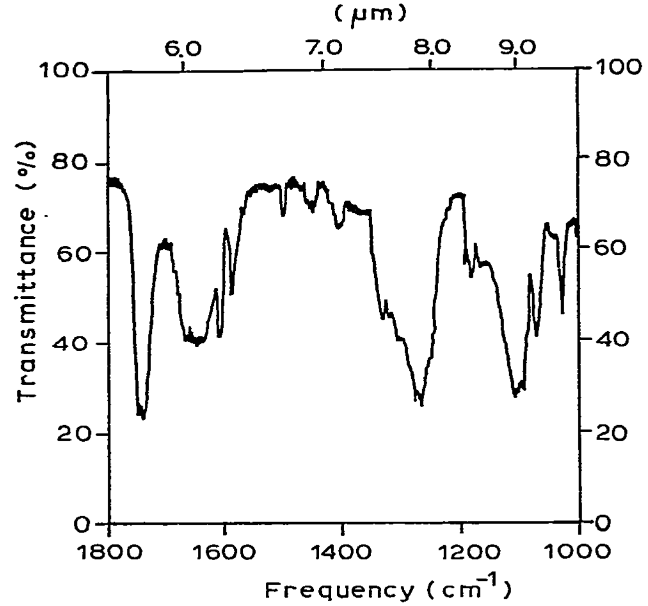

Fig. 3. I.r. spectrum of the α-2–$TiCl_4$ complex.

When conducting the reaction with a twofold quantity of titanium tetrachloride and precipitating the complex with petroleum ether, a compound having the composition **1** · $2TiCl_4$ (complex III) was obtained. Its decomposition gave **2**. In the i.r. spectrum of complex III (Fig. 2), the intensity of the shifted carbonyl-band at 1630 cm^{-1} was increased as compared with the original band at 1730 cm^{-1} and, as with the 1:1 complex, the new band at 1520 cm^{-1} is also present.

On comparing the i.r. spectrum (Fig. 3) of the 1:1 α-**2**–$TiCl_4$ complex (complex IV) with that of complex I (Fig. 1), a difference is found in the shape, and also slightly in the position, of the shifted carbonyl-band appearing between 1680 and 1620 cm^{-1}. Moreover, the intensity ratio is also different from that of the non-shifted band. It is important to note that the band at 1520 cm^{-1} is absent from the spectrum in Fig. 3. It follows from these results that, although the sugar component of each complex is essentially **2** (see chlorine contents of decomposition products given in Table I), the Lewis-acid component is different: in complex IV, it is $TiCl_4$, whereas in complexes I–III, it is presumably benzoyloxytitanium trichloride ($BzOTiCl_3$), the 1520-cm^{-1} band being characteristic of the latter compound.

To support this assumption, $BzOTiCl_3$, not yet described in the literature, was prepared by analogy with the synthesis[3] of $AcOTiCl_3$. Its i.r. spectrum (Fig. 4) shows a characteristic band at 1520 cm^{-1}, which may also be clearly seen in the spectra of complexes I and III (Figs. 1 and 2) in which, because of complex formation, the band of $BzOTiCl_3$ at 1560 cm^{-1} is shifted towards lower wavenumbers and overlaps a band characteristic of the complex.

The progress of the reaction may be continuously monitored by i.r. investiga-

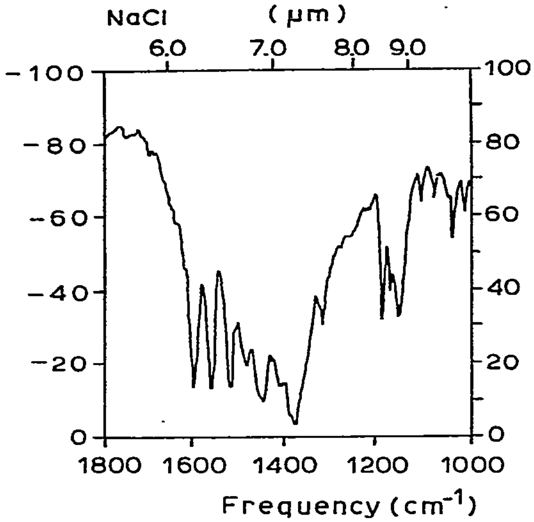

Fig. 4. I.r. spectrum of $BzOTiCl_3$.

tion of a chloroform solution that contains no petroleum ether. Immediately after mixing, the band at 1520 cm^{-1} (characteristic of $BzOTiCl_3$) appears, and a band, gradually increasing in intensity with time, is seen at 1110 cm^{-1}. According to our assumption, this band is to be attributed to the α-C-1–H vibration, and indicates the conversion (anomerization) of *β*-**2** into α-**2**.

From these investigations, it may be concluded that the chlorinated product, which is **2** on the basis of its chlorine content, is rapidly formed in the reaction and is accompanied by a by-product, presumably $BzOTiCl_3$. The first chlorinated product is *β*-**2**, and the α anomer (α-**2**) is only formed later. On the basis of these findings, compound *β*-**2**, thus far unknown[4], has been prepared by applying kinetic control.

Preparation of the complexes of peracylated, mixed glucopyranose esters. — Compounds *β*-**1** and *β*-**3** contain five, apparently equivalent, substituents of equatorial disposition, and hence titanium tetrachloride might form complexes with any of them. Theoretically it is conceivable that $TiCl_4$ could be attached with equal probability to all five acyl groups. It is even possible that an equilibrium is established between them, and that the reaction proceeding with the C-1 complex goes to completion. However, the very rapid formation of the 1-chloro product makes this rather improbable.

In the i.r. spectra of the titanium tetrachloride complexes of *β*-**3** and *β*-**1**, the single acetyl or benzoyl groups cannot be distinguished from one another. Therefore, compounds were synthesized having one benzoyl group and four acetyl groups; these were 2,3,4,6-tetra-*O*-acetyl-1-*O*-benzoyl-*β*-D-glucopyranose, 2,3,4,6-tetra-*O*-acetyl-1-*O*-benzoyl-α-D-glucopyranose, 1,2,3,4-tetra-*O*-acetyl-6-*O*-benzoyl-*β*-D-glucopyranose; and subsequently the 1:1-molar complexes of these compounds with $TiCl_4$ were prepared (complexes V, VI, and VII).

TABLE II

CHARACTERISTIC ESTER BANDS IN THE I.R. SPECTRA OF THE ESTERS OF D-GLUCOSE PREPARED

Compound	$\nu_{C=O}$ *(cm^{-1})*	ν_{as}^{C-C-O} *(cm^{-1})*
Penta-*O*-acetyl-β-D-glucopyranose	1750	1225
Penta-*O*-benzoyl-β-D-glucopyranose	1730	1275
2,3,4,6-Tetra-*O*-acetyl-1-*O*-benzoyl-β-D-glucopyranose	1760, 1750, 1735	1275, 1240, 1220
2,3,4,6-Tetra-*O*-acetyl-1-*O*-benzoyl-α-D-glucopyranose	1760, 1750	1275, 1230
1,2,3,4-Tetra-*O*-acetyl-6-*O*-benzoyl-β-D-glucopyranose	1765, 1715	1285, 1225

The i.r. spectra of the parent compounds (Table II) show that the carbonyl bands are well separated in these mixed esters; thus in the spectrum of 2,3,4,6-tetra-*O*-acetyl-1-*O*-benzoyl-β-D-glucopyranose, the band at 1735 cm^{-1} corresponds to the $\nu_{C=O}$ vibration of the benzoyl group. In the spectrum of the complex of this compound, the $\nu_{C=O}$ bands arising from the acetyl groups appear at 1752 cm^{-1}, and are merged. The band of the substrate at 1735 cm^{-1} (characteristic of the benzoyl group) is absent, and a band shifted to 1660 cm^{-1} appears instead. It follows that in this case, $TiCl_4$ undergoes complexation with the benzoyl group attached to C-1, whereas no complex formation is detected with any of the four acetyl groups.

In the i.r. spectrum of the $TiCl_4$ complex of 2,3,4,6-tetra-*O*-acetyl-1-*O*-benzoyl-α-D-glucopyranose, the shifted carbonyl-band appears at 1670 cm^{-1}; unambiguous assignment of the acyl group linked to $TiCl_4$ is difficult.

The i.r. spectrum of the $TiCl_4$ complex of 1,2,3,4-tetra-*O*-acetyl-6-*O*-benzoyl-β-D-glucopyranose shows a decrease in the intensity of the band at 1765 cm^{-1} (acetyl $\nu_{C=O}$), unchanged intensity of the band at 1715 cm^{-1} (benzoyl $\nu_{C=O}$), and the strong, shifted band at 1658 cm^{-1}; all of these results indicate that $TiCl_4$ is attached to an acetyl group.

The experimental results obtained with the mixed esters suggest that, in β-anomers, $TiCl_4$ is always linked to the 1-acyloxy group, and this assumption may perhaps be extended to all 1,2-*trans*-acylated sugars. This course of the reaction is not readily explained; it may be due to steric reasons or to effects of charge distribution, and consideration must be taken of the fact that the anomeric center is the most favorable site for build-up of positive charge[9]. Neighboring-group effects may also play a part; the 2-*O*-acyl group may polarize the carbonyl group of the C-1 acyl group, thus making O-1 still more nucleophilic. In any event, complex formation at the 1-acyl group evidently promotes the departure of the 1-*O*-acyl group and the progress of the chlorination reaction.

Catalysis of anomerization by $BzOTiCl_3$ derivatives containing substituted benzoic acid. — The by-product in the chlorination reaction of $TiCl_4$ and β-**1** is

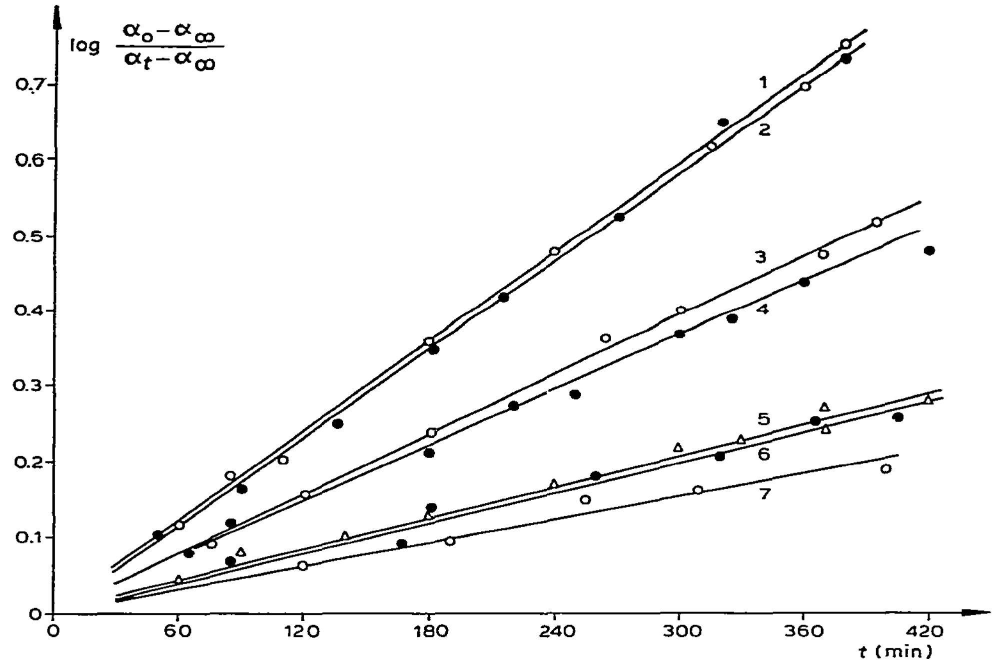

Fig. 5. Anomerization of β-4 in chloroform solution at 25° in the presence of substituted $BzOTiCl_3$ derivatives. Substituents: 1, p-NO_2; 2, m-NO_2; 3, p-Cl; 4, m-Cl; 5, p-CH_3; 6, H; and 7, p-OCH_3.

TABLE III

ANOMERIZATION OF β-4 IN CHLOROFORM SOLUTION AT 25° IN THE PRESENCE OF BENZOYLOXYTITANIUM TRICHLORIDES[a] SUBSTITUTED IN THE AROMATIC RING

Substituent	k × *10³(min⁻¹)*		*log(k/k₀)*
—	0	1.61[b]	0
p-CH_3	−0.170	1.67	0.016
p-OCH_3	−0.268	1.17	−0.139
p-Cl	0.227	3.01	0.272
m-Cl	0.373	2.76	0.234
m-NO_2	0.710	4.39	0.436
p-NO_2	0.778	4.50	0.446

[a] Concentrations: β-4 = 5.453×10^{-2} mol/L; $BzOTiCl_3$ = 5.276×10^{-2} mol/L. [b] When the concentration of $BzOTiCl_3$ was 2.638 mol/L, $k \times 10^3 = 0.82$ min⁻¹.

$BzOTiCl_3$, which, by analogy with $AcOTiCl_3$, must play a role in the anomerization reaction[5] β-2→α-2. To compare the catalytic action of $BzOTiCl_3$ and $AcOTiCl_3$, anomerization has been studied in the conversion of 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl chloride (β-4) into 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl chloride (α-4). $BzOTiCl_3$ was prepared in chloroform solution from benzoic acid and $TiCl_4$,

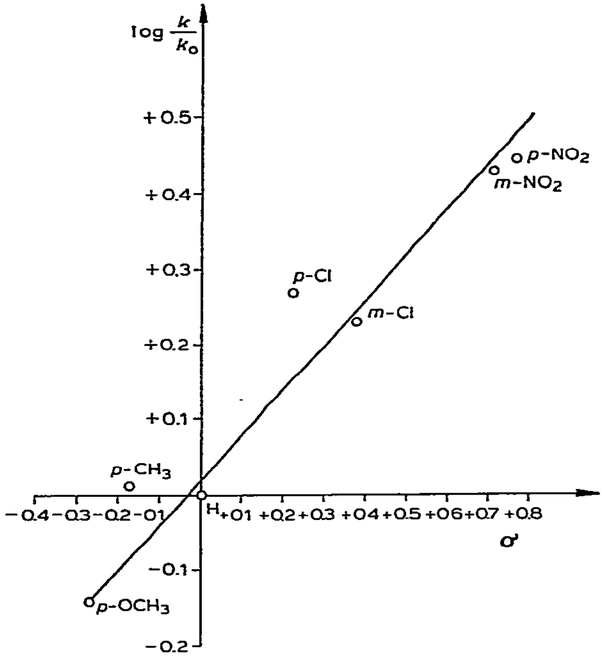

Fig. 6. Anomerization of β-4 in chloroform solution at 25° in the presence of substituted $BzOTiCl_3$ derivatives.

and this solution was allowed to react with an equimolar solution of α-4 in chloroform. Substituted derivatives of benzoic acid were also used. The anomerization reaction was monitored polarimetrically (Fig. 5), and the k-values are recorded in Table III. The k-values[5] for $AcOTiCl_3$ and $BzOTiCl_3$ (1.66×10^{-3} and 1.61×10^{-3} min^{-1}, respectively) are almost the same. In the case of $BzOTiCl_3$ derivatives containing a substituted benzoyl group, anomerization catalyzed by *m*- and *p*-nitrobenzoyloxytitanium trichloride is the most rapid, and that catalyzed by the *p*-methoxybenzoic acid derivative is the slowest. Thus, electron-withdrawing substituents accelerate the reaction, whereas electron-releasing substituents have a decelerating action, as compared with the non-substituted compound. Evidently, electron-attracting groups increase the electrophilic character of the Ti atom. On plotting the values of log k/k_0 as a function of the Hammett σ values, a straight line is obtained, to a close approximation (Fig. 6). The value of the reaction constant (ρ) calculated from the slope of the straight line is +0.6.

EXPERIMENTAL

Materials and methods. — The preparation of the complexes and the method for their investigation have been described in an earlier communication[2]. I.r. spectra were recorded with Zeiss Model UR 10 and Perkin–Elmer Model 237 instruments.

Compounds α-**2** (ref. 1), 2,3,4,6-tetra-*O*-acetyl-1-*O*-benzoyl-α-D-glucopyranose[6], 2,3,4,6-tetra-*O*-acetyl-1-*O*-benzoyl-β-D-glucopyranose[7], and 1,2,3,4-tetra-*O*-acetyl-6-*O*-benzoyl-β-D-glucopyranose[8] were prepared as described in the literature.

*2,3,4,6-Tetra-*O*-benzoyl-β-D-glucopyranosyl chloride* (β-**2**). — Compound β-**1** (10 g, 14.3 mmol) was dissolved in 56 mL of hot chloroform, previously dried over calcium chloride. The solution was cooled to room temperature and, under shaking, 1.7 mL (2.93 g, 15.4 mmol) of $TiCl_4$ dissolved in 5 mL of chloroform was added. The mixture was shaken for 1–2 min, and then poured into 100 mL of ice–water, and the organic phase rapidly washed with 45 mL of ice–water. The chloroform solution was dried over sodium sulfate, and evaporated in vacuum on a water bath at 40°. The residue was crystallized from ether–petroleum ether, to give 5.2 g (59.2%) of white, crystalline product, m.p. 107–109°. Recrystallization from ether–petroleum ether raised the m.p. to 109–111°; $[\alpha]_D^{20}$ +46.7°.

Anal. Calc. for $C_{34}H_{27}ClO_9$: C, 66.40; H, 4.39; Cl, 5.89. Found: C, 66.70; H, 4.74; Cl, 5.90.

Benzoyloxytitanium trichloride. — To a solution of 5.31 mL (9.17 g, 48 mmol) of $TiCl_4$ in 6 mL of dry chloroform was added dropwise, with stirring, a solution of 2 g (0.016 mol) of dried benzoic acid in 10 mL of chloroform. After 15 min, 20 mL of dry petroleum ether was added to the mixture containing a precipitate, and the latter was then filtered off. The precipitate was washed four times with petroleum ether and dried in a vacuum-desiccator over paraffin flakes, sodium hydroxide, and phosphorus pentaoxide; yield, 4.1 g.

Anal. Calc. for $C_7H_5Cl_3OTi$: Cl, 38.63; Ti, 17.4. Found: Cl, 38.68; Ti, 16.70.

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