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# THE STERIC COURSE OF THE REACTIONS OF 2,3-DIHALOTETRAHYDROPYRANS WITH GRIGNARD REAGENTS

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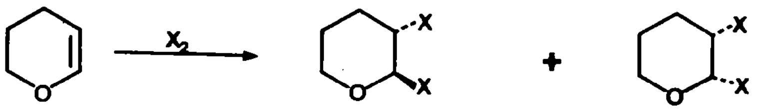
**Abstract.** The steric course of some reactions of 2,3-dihalotetrahydropyrans with sodium methoxide and with methyl- and phenyl-magnesium bromides has been reinvestigated. Whereas the methanolysis of the cis- and trans-dichlorides occurs with practically complete inversion, it has been confirmed that their reactions, as well as those of the dibromides, with methylmagnesium bromide are non-stereospecific, yielding mixtures of trans- and cis-3-halo-2-methyl-tetrahydropyrans in ratios that are independent of the configurations of the starting dihalides. It has been further established that Grignard reagents cause equilibration of cis- and trans-dihalide mixtures in a reaction that is much faster than the Grignard coupling step.

A halogen atom α to the tetrahydropyran oxygen is know to be easily replaced by alkyl or aryl groups in the reaction with Grignard reagents, as generally occurs with α-halo ethers.[1] This type of reaction, if applied to protected glycosyl bromides, could provide an easy access to C-glycosides, a class of compounds that has recently been receiving much attention, owing to their biological interest.[2] Relatively little information is however available in the carbohydrate literature on its application, apart from older work by Hurd and co-workers[3] and from one recent paper.[4] The reaction of 1,2-dideoxy-1,2-dihalopyranoses, easily available by addition of halogens to glycals, could offer an interesting and simple approach to 2-deoxy-2-halo-C-pyranosides of potential synthetic interest. Since no data were available in the literature on reactions of the latter type in the carbohydrate field, some years ago we started an investigation on the steric course of the model reaction of 2,3-dihalotetrahydropyrans with Grignard reagents, for which only qualitative results were available, and presented preliminary results at a local meeting in 1979.[5] The recent publication of an extensive study on the same topic[6] induces us to present our results, that in part confirm and in part integrate the data of that paper.

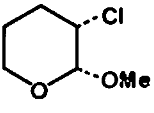
The addition of chlorine to **1** is known to give trans- and cis-dichlorides **2** and **3** in ratios that depend roughly on the solvent polarity: Stone and Daves[7] reported ratios of the chlorine adducts **2** and **3** ranging between 18:82 in pentane and 64:36 in THF, as determined by NMR analysis of the crude product. We found this method unsatisfactory owing to some overlap of the anomeric proton signals on which the analysis was based, as had also been reported in older work by Lemieux and Fraiser-Reid.[8] We therefore determined the compositions of the dichloride mixtures after reaction with sodium methoxide in methanol to yield the corresponding cis- and trans-3-chloro-2-methoxytetrahydropyrans **6** and **7** that are easily analyzed by NMR.[9] The assumption that this reaction proceeds via an $S_N2$ mechanism with complete inversion was first made by Lemieux and Fraiser-Reid[8] who used methanol and $Ag_2CO_3$ for the solvolysis of **2**+**3**. Stone and Daves[7] who used sodium methoxide in DMF reported complete inversion of **3** into **7**, accompanied by 20% elimination to **8**, and predominant inversion of **2** to **6** and **7** (80:20), with no elimination. Recently Crombie and Wyvill[6] described a preparative conversion of a ca. 50:50 mixture of **2**+**3** into a 78:22 mixture of **6**+**7** with sodium methoxide in methanol, but analysis was made on a distilled product (57% yield),



1

2: X= Cl
4: X= Br

3: X= Cl
5: X= Br



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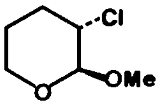

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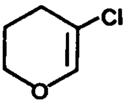

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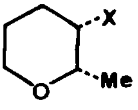
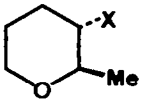


9: X=Cl
15: X=Br



10: X=Cl
16: X=Br

that probably did not correspond in its composition to that of the crude reaction product, owing to fractionation. In our hands the same reaction, carried out on a presumably identical mixture of 2+3 (obtained from 1 with chlorine in ether), in which the crude product was directly analyzed by NMR, gave a 49:51 ratio of 7:6, and no elimination product 8. Similarly the addition product of HCl to 8, reported[7,10] to be pure 2, produced 6+7 in a ratio of ca. 95:5, ensuring at least 95% inversion, but probably more since the NMR spectrum of the starting sample of 2 showed some qualitative evidence for the presence of a small amount of 3. The comparative data given in Table 1 support the assumption that the ratios of 6 to 7 formed with MeONa in MeOH reliably reflect the ratios of 2 and 3.

**Table 1.** Analysis of 2 + 3 mixtures

| Conditions of preparation | trans/cis ratios<br>by methanolysis with MeONa/MeOH[a] | by methanolysis with MeOH/$Ag_2CO_3$[b] | by direct NMR determination | |
|---|---|---|---|---|
| 1 + $Cl_2$ ($Et_2O$ or $CCl_4$) | 49:51 | 50:50 | 34:66[c] | 50:50[d] |
| 8 + HCl ($C_6H_6$) | 95: 5 | ----- | 100: 0[c] | ----- |
| Equilibration ($TiCl_4/C_6H_6$) | 72:28 | 70:30 | 65:35[c] | ----- |
| Equilibration ($Et_4NCl$/MeCN) | ----- | ----- | ----- | 80:20[d] |

[a] Our work; [b] Ref. 8; [c] Ref. 7; [d] Ref. 6.

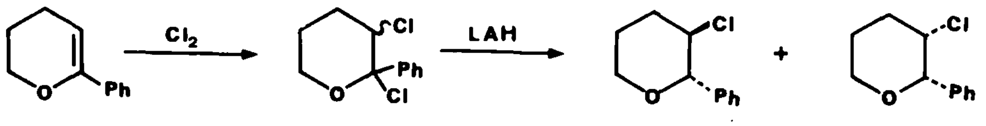
The reaction of a mixture of 2 and 3 of undefined composition with methylmagnesium bromide was reported by Riobé[11] who separated 9 and 10 by distillation and correctly attributed their configurations on the basis of the Auwers-Skita rule and to their behaviour with base, but did not provide an exact data on their ratio. An exact knowledge of the composition of 2+3 mixtures turned out to be relatively unimportant for our purposes when it was found that three mixtures ranging from about 50:50 to 95:5 (Table 1), when reacted with methylmagnesium bromide gave products of identical composition in which cis- and trans-3-chloro-2-methyl derivatives 9 and 10 were present in a ratio of 57:43. A similar observation was made by Crombie and Wyvill[6] for the reaction of **2+3** with several alkylmagnesium bromides: they yielded cis- and trans-2-alkyl-3-chlorotetrahydropyrans in ratios that depended on the bulk of the alkyl group, but were independent of the initial **2+3** ratio. When the reagent was MeMgBr a 1:1 mixture of **2+3** was reported to give a 68:32 ratio of **9+10**. It was also found that when $Me_2Mg$ was used as the reagent this ratio changed to 33:67. The not very relevant difference between our and Crombie's results may be due to the presence of some $Me_2Mg$ in our reagent. We further found that when the reaction mixtures of **2+3** with MeMgBr were analyzed before complete conversion by quenching with sodium methoxide in methanol in order to analyze for unreacted dihalides, no matter how far the reaction had progressed and independently of the **2+3** ratio in the starting material, the ratio of **6+7** was constantly 75:25 (Table 2), pointing to a rapid equilibration of **2+3** to dihalides with a trans/cis ratio of 75:25 (possibly with partial or total conversion to 2-bromo-3-chloroderivatives by halogen interchange with the Grignard reagent), in a reaction that is much faster than the Grignard coupling step: for instance in a reaction conducted for 1 hr at 0°C, only about 10% of the products **9** and **10** had formed, but the remaining dihalides already had reached equilibrium. Magnesium bromide which could be present in the reaction medium, owing to the Schlenk equilibrium, produced equilibration at a much slower rate, so that the actual efficient equilibrating agent is very likely the Grignard reagent itself.

**Table 2.** Composition of partial reaction mixtures of **2+3** with MeMgBr.

| Starting 2:3 ratio | Temperature | Reaction time (min.) | **9:10** ratio | Unreacted 2:3 ratio | % Conversion of **2+3** into **9+10** |
|---|---|---|---|---|---|
| 50:50 | 0°C | 60 | 58:42 | 75:25 | 10 |
| 50:50 | 20°C | 10 | 56:44 | 75:25 | 66 |
| 95: 5 | 20°C | 10 | 57:43 | 75:25 | 69 |
| 72:28 | 20°C | 60 | 56:44 | 75:25 | 90 |

The reaction of **2** and **3** with phenylmagnesium bromide has been reported to give exclusively trans-2-phenyl-3-chlorotetrahydropyran **13**.[6,7,12] We repeated this reaction both on the 1:1 and on the 95:5 mixtures of **2** and **3** and obtained crude products which, when analysed by GLC, showed that by far the main constituent was the trans isomer **13**; a small peak with the same retention time as the cis isomer **14**, (ca. 2% with respect to the trans isomer) was detected too. When the reaction was quenched before completion, the ratio of unreacted **2** and **3** was found to be 77:23. The unknown cis-2-phenyl-3-chlorotetrahydropyran **14** was prepared for comparison through the sequence shown in the Scheme 1, that produced a mixture of **13** and **14** in a ratio of 24:76.

**Scheme 1**



**11** **12** **13** **14**

Mixtures of the trans- and cis-dibromides **4** and **5** were obtained by addition of bromine to

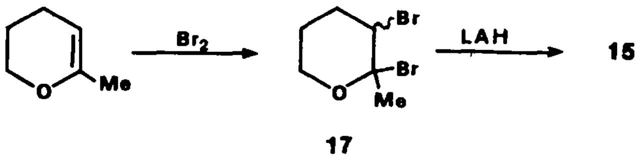
1 at -25°C in different solvents (Table 3). They were even less stable than the dichlorides, but direct analysis by NMR was possible in this case since the H-2 signals of the two diastereomers were sufficiently separated. The ratios **4**:**5** ranged between 67:33 in $CCl_4$ and 86:14 in dioxane (Table 3) and changed to 94:6 after equilibration with tetrabutylammonium bromide in $CCl_4$. The composition of the product obtained in $CCl_4$ was significantly different from the previously reported one[8] (an 89:11 ratio of **4+5**) but the latter product had been distilled before analysis and this may have caused partial equilibration. A ratio of 88:12 was reported for a product prepared in ether at 0°C.[6]

**Table 3.** Analysis of **4+5** mixtures obtained from **1** with $Br_2$

| Solvent and temperature | trans/cis ratios |
|---|---|
| $CCl_4$ (-25°C) | 67:33 |
| $C_6H_{12}$ (-20°C) | 69:31 |
| $Et_2O$ (-25°C) | 74:26 |
| Dioxane (5°C) | 86:14 |
| Equilibration ($Bu_4NBr$, $CCl_4$, 20°C) | 94: 6 |

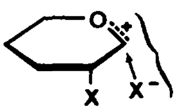
Also the reaction of **4+5** mixtures with methylmagnesium bromide gave cis- and trans-3-bromo-2-methyltetrahydropyran (**15** and **16**) in a constant ratio (24:76) independently of the ratios of the dibromides in the starting materials. This reaction has been previously reported;[13] but no mention was made of the formation of diastereomers. A slightly different ratio of **15** and **16** (18:82) was reported by Crombie and Wyvill.[6] We isolated pure trans compound **16** from the crude reaction product, and a reference sample of the cis isomer **15** was prepared through the sequence of Scheme 2.

**Scheme 2**

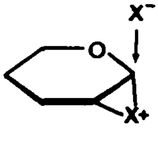


## DISCUSSION

The steric course of the addition of halogen to **1** and to glycal acetates has been repeteadly discussed on the basis of a first proposal by Lemieux and Fraiser-Reid,[8] later elaborated by Igarashi, Homma and Imagawa,[14] Boullanger and Descotes[15] and Stone and Daves.[7] Variations of adduct composition were attributed mainly to different contributions of two mechanisms, one involving



**18**



**19**

the collapse of a tight ion pair (**18**) in less polar solvents to give mainly the cis-adduct, the other a reaction of a solvent stabilized halocarbonium or epihalonium ion (**19**) yielding preferentially the trans adduct. We have found that also in the bromine addition to **1** on passing from less to more polar solvents (Table 3) the ratio of trans to cis dihalides increases and that for the same solvent this ratio is significantly higher than that found for the corresponding dichlorides. This can well be explained by the higher bridging capability of bromine with respect to chlorine, favouring the contribution from the pathway involving anti attack on the epibromonium ion **19** (X=Br).

A point of major interest arising from our work is the efficiency of the Grignard reagent in promoting equilibration of the 2,3-dihalotetrahydropyrans. The fact that the scarcely ionized reagents R-Mg-X are much better equilibrating agents than the more highly ionic $MgBr_2$ could be accounted for by assuming the concerted exchange of halogen atoms within a complex originating from replacement of one of the magnesium solvating ether molecules by a dihalotetrahydropyran one. On the other hand the steric course of the slow Grignard coupling reaction of the dihalides cannot be interpreted in straighforward terms of stereospecific retention or inversion, since the ratios of 2-methyl-3-halo derivatives do not reflect the composition of the equilibrated dihalide mixtures, but rather depend on the type of halogen and Grignard reagent, and consequently on different contributions of intermediates of type **18** and **19** in an $S_N1$-type mechanism. The observation that the cis/trans ratios of the products of the reactions with MeMgBr are rather close to those obtained in the halogen additions to **1** in ethyl ether (Table 4) supports such a mechanism and could imply that the same carbonium or halonium intermediates **18** and **19** are involved in both types of reactions and undergo nucleophilic attack by halide ion in one case and by alkyl anion equivalent in the other.

**Table 4.** Comparison between halogen additions in ethyl ether and Grignard coupling reactions

| Reaction | cis/trans ratio of products |
|---|---|
| **1** + $Cl_2$ | 51:49 |
| **2**+**3** + MeMgBr | 57:43 |
| **1** + $Br_2$ | 26:74 |
| **4**+**5** + MeMgBr | 24:76 |

The recent data[6] showing a significant shift towards higher trans/cis ratios when passing from RMgBr to $R_2Mg$ could possibly be attributed to a lesser dihalide equilibrating ability of the latter reagent. Unfortunatly these experiments were carried out only on one mixture of **2**+**3**.

The reaction of **2**+**3** with $C_6H_5MgBr$, giving almost exclusively the trans product, does not fit this scheme, but could be caused by the larger bulk of the phenyl group. The recent study[6] of the coupling of **2**+**3** and **4**+**5** with several different Grignard reagents shows a definite trend of decreasing cis/trans product ratios with increasing size of the R group of the reagent, from 68:32 for R = methyl to about 33:67 for R = isopropyl or cyclohexyl. However the 2:98 ratio we find for R = phenyl can hardly be justified by size alone since the latter substituent cannot be considered much larger than isopropyl or cyclohexyl. The peculiar character of the aryl group must therefore also play a significant role. It may also be mentioned that the reaction of 2-acetyl-3,4,6-tri-O-benzyl-α-D-galactopyranosyl bromide with vinylmagnesium bromide was reported to give an 85% yield of the β-vinyl-C-glycoside, no mention being made of the formation of any α-anomer.[16]

Older work[3] on the reaction of 2,3,4,6-tetra-O-acetyl-α- and -β-D-glucopyranosyl chlorides with $C_6H_5MgBr$ reported the formation of the 1-phenyl derivatives in an identical α/β anomer ratio of 3:7 from both anomeric chlorides, in accordance with a preequilibration step, but the complications connected with the similar rates of Grignard coupling and of attack by the reagent on the acetoxy groups makes any interpretation uncertain, since more than one species probably is involved in the glycosidic C-C bond forming step. A recent repetition of this reaction reported only the formation of the β-phenyl glycosides, no mention being made of α-anomer.[4] On the other hand the conformationally rigid r-3-acetoxy-c-6-bromo-t-2-tert-butyltetrahydropyran was found to be attacked with prevalent retention,[17] pointing to preferential axial attack at carbon 2, when position 3 does not carry a substituent providing assistance, in analogy with what was found for Grignard reactions of 2-alkoxy-1,3-dioxanes.[18]

The results reported in this paper may be of interest as a basis for a wider utilization of Grignard reagents in stereoselective syntheses of C-glycosides.

## EXPERIMENTAL

NMR spectra were determined on ca. 10% solutions in $CDCl_3$ (unless stated otherwise) on Jeol C-60 HL or Varian CFT-20 spectrometers. GLC analyses were run on a Carlo Erba Fractovap GV and a Perkin-Elmer F-11, both equipped with flame ionization detectors, under the following conditions: **A**:2.5-m glass column filled with 3% OV-17 on 80-100 mesh silanized Chromosorb W, $N_2$ flow 45 ml $min^{-1}$; column temperature 75°C; **B**: 3-m glass column filled with 1% SE 52 on 80-100 mesh silanized Chromosorb W, $N_2$ flow 30 ml $min^{-1}$, column temperature 65°C; **C**:same conditions as **B** but with programmed temperature, low isotherm 75°C for 7.5 min, then 5°C $min^{-1}$ up to 180°C. All comparisons between the compounds described in this paper and those prepared according to literature data were made on the basis of IR and NMR spectra and GLC retention times.

**trans- and cis-2,3-Dichlorotetrahydropyran (2 and 3).** A 10% solution of 3,4-dihydro-2H-pyran (**1**) in dry ether was treated with gaseous $Cl_2$ at 0°C until a green-yellow colour persisted, excess $Cl_2$ was eliminated by addition of one drop of **1**, the solvent was eliminated in vacuo at room temperature and the residue stored at -30°C. Great care was taken in working under perfectly anhydrous conditions. The NMR spectra of the crude residue in $C_6D_6$ showed a narrow signal at δ 5.92 for H-2 of **2**, and a doublet (J = 3 Hz) at δ 5.86 for H-2 of **3**, that partly overlapped, thus preventing an accurate quantitative evaluation of the **2**/**3** ratio. Analysis by methanolysis (see below) showed that **2** and **3** were present in an about 1:1 ratio.

A sample of the trans-dichloride **2** was also prepared according to Stone and Daves[7] by addition of HCl to **8** in benzene. Its NMR spectrum showed a strong signal at δ 5.92 for **2**, but a small shoulder on the high-field side of this signal pointed to the presence of a small amount of **3**. This was confirmed by methanolysis analysis that gave a 95:5 ratio of **2**:**3**.

Samples of the products of the above two reactions were equilibrated under the following conditions: the **2**+**3** mixture (1 mmole) and $TiCl_4$ (0.1 ml) in dry benzene (15 ml) were shaken at room temperature for a given time, then analysed by methanolysis. Reaction times of 15 min and 5 hr produced dichlorides having the same 72:28 trans/cis ratio. No modification occurred in a 1:1 mixture of **2**+**3** in benzene when dry HCl was bubbled through it for 2 hr at room temperature.

The solution of the 1:1 mixture of **2** and **3**, obtained by $Cl_2$ addition to 5 mmole of **1** in ether (5 ml), was added to a solution of anhydrous $MgBr_2$, prepared according to Rowley[19] from Mg (3.75 mmole) in ether (5 ml). After 20 min at 23°C the reaction was quenched with MeONa for analysis via the methoxy derivatives: the composition of the trans/cis dihalide mixture had changed to 58:42, being still far from the ratios observed in the equilibrations with MeMgBr and with $TiCl_4$.

**Analysis of the dichloride mixtures by methanolysis.** A ca. 1M solution of the dichlorides (10 mmole) in ether or benzene was treated dropwise at 0°C with a MeONa solution prepared from Na (11.5 mmole) and MeOH (20 ml), stirred 1 hr at room temperature, then treated with solid $NaHCO_3$, stirred 30 min, filtered. The filtrate was evaporated to dryness in vacuo and analysed by GLC and NMR. GLC (conditions **B**) proved the absence of side-products, such as **8**, but no good conditions were found for a sharp separation of the peaks of the methoxy derivatives **6** and **7** that were better analysed by integration of the well separated NMR doublets of the anomeric protons centered at δ 4.40 ($J_{2,3}$ = 4 Hz) and 4.59 ($J_{2,3}$ = 3 Hz), respectively for **7** and **6**, in accordance with previous literature.[6-10] The absence of a signal at $\delta$ 6.57 for H-2 of **8** confirmed that this elimination product had not formed. The **6**:**7** ratio corresponds to the 2:3 ratio in the starting material if complete inversion during methanolysis is assumed.

**trans- and cis-2,3-Dibromotetrahydropyrans (4 and 5).** Addition of an equimolar amount of bromine was carried out at -25°C on 1M solutions of **1** in the given dry solvent under dry nitrogen. The resulting products were analysed directly by NMR in the reaction solutions, when possible ($CCl_4$, cyclohexane), or after evaporation of the solvent in vacuo at room temperature (ether, dioxane). The **4**:**5** ratio was obtained by integration of the corresponding anomeric proton signals at $\delta$ 6.75 ($W_{½}$ = 4.5 Hz) and 6.53 ($W_{½}$ = 6 Hz)[8] (Table 3).

Equilibration was rapidly achieved (20 min) by addition of tetrabutylammonium bromide to the $CCl_4$ solution of **4**+**5** in the NMR tube.

**Reactions of the dichlorides 2 and 3 with MeMgBr.** A solution of MeMgBr prepared from Mg (150 mmole) and MeBr (168 mmole) in ether (100 ml) was cooled at -20°C and treated under stirring with a solution of the dichlorides **2** and **3** freshly prepared by $Cl_2$ addition to **1** (120 mmole) in dry ether (100 ml). Stirring was continued at -20°C for 10 min, then at room temperature for 2 hr. An excess of saturated aqueous $NH_4Cl$ was added, the organic phase was dried and evaporated to give a residue (12 g, 75%) consisting of a mixture of **9** and **10** in a ratio of 57:43 (GLC, conditions **B**). Distillation through a spinning band column allowed separation of **10**, b.p. 58-59°C/22 mmHg, $n_D^{20}$ 1.4550 (lit.[11] b.p. 56°C/23 mmHg, $n_D^{21}$ 1.4543) from **9**, b.p. 77-78°C/22 mmHg, $n_D^{20}$ 1.4654 (lit.[11] 72°C/23 mmHg, $n_D^{21}$ 1.4642). The NMR spectra of the two isomers were in accordance with the reported data.[9]

A series of runs were conducted on the 10 millimolar scale with different mixtures of **2** and **3** under conditions of uncomplete conversion. The reaction was interrupted by cooling to 0°C and slowly adding MeONa (11 mmole) in MeOH (20 ml) and stirring 1 hr at room temperature, followed by addition of solid $NaHCO_3$. The slurry was filtered and the filtrate evaporated in vacuo. Analysis was carried out by GLC (conditions **B**), that gave the ratio of **10**:**9**:**7**+**6** (relative retention times 1:1.51:1.99:2.12). A more accurate evaluation of the **7**:**6** ratio was possible by NMR analysis. The data for some of the runs are given in Table 4.

**Reactions of the dibromides 4 and 5 with MeMgBr.** The reaction of the mixture of the dibromides **4** and **5**, freshly prepared by addition of $Br_2$ (0.76 mole) to **1** (0.75 mole) in ether, with MeMgBr was carried out as described by Brandon.[13] The crude product was a 24:76 mixture of **15** and **16** (GLC, conditions **A**; relative retention times 2.14:1). Fractional distillation afforded **16** of about 95% purity, b.p. 69-75°C/20 mmHg (lit.[13] b.p. 60-61°C/17 mmHg). A pure sample of **16** was obtained by chromatography on neutral alumina (act. I, elution with hexane). Its characterization as the trans isomer **16** had been previously[20] reported on the basis of its high-yield conversion into 2-methyl-5,6-dihydro-2H-pyran, and was confirmed by the close similarity of its NMR spectrum to that of the corresponding chloro derivative **10**.

Similar reactions were carried out on the 10 millimolar scale with two mixtures of **4** and **5** having different compositions, respectively obtained by addition of $Br_2$ to **1** in cyclohexane (69:31 ratio of **4**:**5**), and by equilibration with tetrabutylammonium bromide (94:6 ratio). The Grignard reagent addition was carried out at -25°C and the reaction mixture was left 3 hr at room temperature, before quenching with $NH_4Cl$ solution. The crude product was extracted with ether and analysed by GLC. The ratio of **15** to **16** was in both cases 24:76.

**cis-3-Bromo-2-methyltetrahydropyran (15).** 2-Methyl-5,6-dihydro-4H-pyran[21] (2 g, 20 mmole) in dry ether (50 ml) was cooled at -20°C and slowly treated with $Br_2$ (20.1 mmole). The dibromo derivative **17** was very unstable and lost HBr above 0°C. An NMR spectrum, taken on an evaporated sample, showed that the trans form of **17** was by far the main product on the basis of a narrow signal at $\delta$ 4.6 for an equatorial proton at C-3. Cis-**17** would expected to exist mainly in the 2-Br(ax),3-Br(eq) conformation, owing to the anomeric effect. The rest of the solution was treated at -20°C with $LiAlH_4$ (10 mmole) in $Et_2O$ (50 ml). When the reaction mixture had reached room temperature it was refluxed for 3 hr, then treated with $H_2O$ (0.4 ml), 3N NaOH (0.4 ml) and $H_2O$ (1.2 ml). Filtration and evaporation gave an oily residue that contained **15** and **16** in a ratio of about 9:1 (GLC, conditions **A**). Chromatography over neutral alumina (act. I, elution with hexane) gave pure **15** as an oil. NMR: $\delta$ 1.23 (d, 3H, J = 6 Hz, C(2)-Me); 3.47 (dq, 1H, J = 6 and 1.5 Hz, C(2)-H); 4.33 (m, $W_{½}$ = 8 Hz, C(3)-H). Elem.Anal.: found% (calcd. for $C_6H_{11}BrO$): C 39.8 (40.2); H 6.5 (6.1); Br 44.3 (44.6).

**Reactions of the dichlorides 2 and 3 with $C_6H_5MgBr$.** Solutions of **2**+**3** (10 mmole of the 1:1 or of the 95:5 mixture) in dry ether (10 ml) were added to a Grignard reagent prepared from bromobenzene (14 mmole) and Mg (15 mmole) in ether (10 ml) and left at room temperature 30 min. Treatment with sodium methoxide as described above, followed by GLC analysis, showed that the reaction was complete, peaks for the methoxy chlorides **6** and **7** being absent. The chromatogram showed, beside a peak for biphenyl (side-product in the Grignard reagent preparation), a strong peak for trans-2-phenyl-3-chlorotetrahydropyran **13** and a very small one (about 2% with respect to **13**) with the same retention time as **14**. A reaction conducted for 10 min gave the same ratio of **13**:**14**, but about 20% of the methoxy chlorides **6** and **7** were present in a ratio of 23:77 corresponding to a ratio of 77:23 of unreacted and equilibrated dihalides **2** and **3**.

A reference mixture of **14** and **13** was obtained as follows: a solution of 2-phenyl-5,6-dihydro-4H-pyran[22] (**11**) (4.75 mmole) in dry ether (7 ml) was treated with a slight excess of chlorine, dry nitrogen was bubbled until the solution become colorless. The unstable dichloride **12** was not isolated, a titrated[23] solution containing 1.3 mmole of $LiAlH_4$ in 10 ml of $Et_2O$ being added immediately at -15°C. The solution was left at this temperature for 30 min, then 30 min at room temperature, finally refluxed for 90 min. After hydrolysis with $H_2O$ and NaOH and evaporation of the ether, the crude residue analysed correctly for 2-phenyl-3-chlorotetrahydropyran: found% (calcd. for $C_{11}H_{13}ClO$) : C 66.9 (67.2); H 6.6 (6.6); Cl 18.1 (18.1). GLC analysis showed that it was composed of two compounds in a ratio of 74:26 (conditions **C**, relative retention times 1.09:1). The minor component had the same retention time as the trans isomer **13**. The NMR spectrum was in accordance with what expected for a mixture of **13** and **14**, the presence of the cis isomer **14** being confirmed by a strong narrow signal at $\delta$ 4.70 for the C-2 proton ($W_{1/2}$ = 4.5 Hz) typical of an equatorial proton. In **13** the corresponding signal was a doublet ($\delta$ 4.25, J = 9.5 Hz). Since the only pourpose of this preparation was to obtain a reference sample for **13**+**14**, and the mode of synthesis and analytical data provided fairly reliable evidence for the structures, no attempt was made to separate a pure sample of **14**.

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