[JOINT CONTRIBUTION FROM THE WM. H. CHANDLER CHEMISTRY LABORATORY, LEHIGH UNIVERSITY, AND THE RESEARCH AND DEVELOPMENT DIVISION, SMITH, KLINE AND FRENCH LABORATORIES]

The Reaction of Grignard Reagents with Lactones. I. Ethyl and Methyl Grignard Reagents with 2,2-Diphenyl-4-butanolactones

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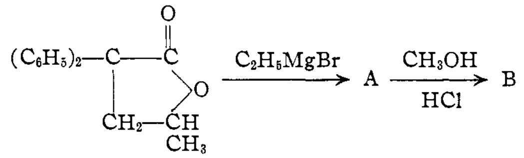
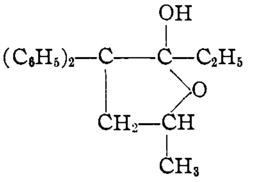
The abnormal reaction of 2,2-diphenyl-4-pentanolactone with ethylmagnesium bromide is shown to give a glycol, which results from both addition of and reduction by the Grignard reagent. This abnormal reaction is also found to occur with 2,2-diphenyl-4-butanolactone. However, methyl Grignard reagent was found to react in a normal fashion with the pentanolactone to give 4,4-diphenyl-5-methyl-2,5-hexanediol. Reduction of 2,2-diphenyl-4-pentanolactone with lithium aluminum hydride gives 2,2-diphenyl-1,4-pentanediol. The 1,4-glycols are readily converted to tetrahydrofuran derivatives with alcoholic hydrogen chloride, and were characterized as acetates.

The reaction between an aliphatic Grignard reagent and a lactone such as butyrolactone proceeds in a normal fashion to form a glycol, which results from the addition of two moles of Grignard reagent.[2] The reaction may be formulated to proceed in a stepwise fashion by the initial formation of a cyclic hemiacetal (*e.g.* II below) which is tautomeric with a hydroxyketone. The second step would then involve the action of another mole of Grignard reagent to give the glycol.

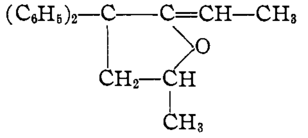
The reaction of ethylmagnesium bromide with 2,2-diphenyl-4-pentanolactone (I) was studied by Wilson,[3] who formulated the product A as the cyclic hemiacetal (II). Wilson dehydrated the product A and assigned to the resulting compound B the structure of 3,3-diphenyl-5-methyl-2-ethylidenetetrahydrofuran (III).



I



II

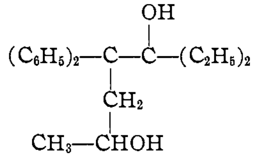


III

Two independent syntheses[4] of compound III by different procedures gave a compound which differed from Wilson's compound B. Therefore, the sequence of reactions reported by Wilson was repeated and the resulting compounds were carefully studied.

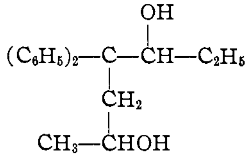
Compound A was found to contain two active hydrogen atoms by the Zerewitinoff determination.[5] Moreover, it was found possible to form a diacetate from A with acetic anhydride and pyridine. (The monoacetate obtained by Wilson was not obtained.) The dehydration product B did not react with bromine, in contrast to cyclic vinyl ethers such as III[4] and α-methylenecoumaran,[6] which readily give bromine substitution products. Oxidation of compound B with potassium permanganate gave benzophenone, which showed that no phenyl rearrangement had occurred. The analytical data showed that compound A could not be the glycol (IV), which would result from the normal addition of two moles of Grignard reagent to the lactone.

Structures V and VI agree well with the analytical data for A and B, respectively, and are compatible with the chemical evidence.



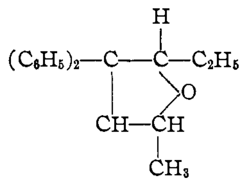
$(C_6H_5)_2C(CH_2CHOHCH_3)\text{—}C(OH)(C_2H_5)_2$

IV

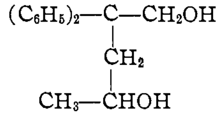


$(C_6H_5)_2C(CH_2CHOHCH_3)\text{—}CH(OH)\text{—}C_2H_5$

V



VI



$(C_6H_5)_2C(CH_2CHOHCH_3)\text{—}CH_2OH$

VII

Reduction of 2,2-diphenyl-4-pentanolactone with lithium aluminum hydride gives glycol (VII) which is characterized by dehydration to 3,3-diphenyl-5-methyltetrahydrofuran and by formation of a diacetate. Spectral data show the similarities between compounds V and VII.

The sequence of reactions used by Wilson was applied to 2,2-diphenyl-4-butanolactone[7] and the abnormal reaction again occurred to give 3,3-diphenyl-1,4-hexanediol, which was transformed to the diacetate and to 3,3-diphenyl-2-ethyltetrahydrofuran.

The reaction of the methyl Grignard reagent with 2,2-diphenyl-4-pentanolactone would not be expected to give the abnormal product as the methyl Grignard reagent is not capable of facile reductions.[8] This reaction proceeds in a normal fashion with the formation of 4,4-dimethyl-5-methyl-2,5-hexanediol, which was characterized by formation of the

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[1] (a) Abstracted in part from the thesis submitted in partial fulfillment of the requirements for the degree of Master of Science; (b) Smith, Kline and French Laboratories.

[2] S. Losanitch, *Compt. rend.*, **153**, 390 (1911); also B. I. Arventi, *Chem. Zentr.*, **114**, II, 718 (1943); *C.A.* **38**, 2338, 5217 (1944).

[3] W. Wilson, *J. Chem. Soc.*, 1993 (1948).

[4] N. R. Easton, S. J. Nelson, V. B. Fish and P. N. Craig, paper presented before the Organic Division, A.C.S. 122nd Meeting, Atlantic City, N. J., Sept. 18, 1952; THIS JOURNAL **75**, 3751 (1953).

[5] P. M. Maginnity and J. B. Cloke, *Anal. Chem.*, **20**, 978 (1948).

[6] R. Adams and R. E. Rindfusz, THIS JOURNAL, **41**, 648 (1919).

[7] J. Attenborrow, J. Elks, B. A. Hems and K. N. Speyer, *J. Chem. Soc.*, 510 (1949).

[8] H. Gilman, "Organic Chemistry," 2nd Ed., Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 647.

monoacetate and by dehydration to 3,3-diphenyl-2,2,5-trimethyltetrahydrofuran.

The isolation and structural determination of intermediates is now being attempted.

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Experimental

4,4-Diphenyl-2,5-heptanediol (V).—The procedure used was identical with that employed by Wilson.[3] After three recrystallizations from methylcyclohexane, the product melted at 123–124°. Active hydrogen was determined by the Zerewitinoff method.[5]

Anal. Calcd. for $C_{19}H_{24}O_2$: C, 80.24; H, 8.51; active hydrogen, 0.704. Calcd. for $C_{19}H_{22}O_2$ (II): C, 80.82; H, 7.86; active hydrogen, 0.356. Calcd. for $C_{21}H_{28}O_2$ (IV): C, 80.72; H, 9.03; active hydrogen, 0.64. Found: C, 80.00; H, 8.51; active hydrogen, 0.83. Found (Wilson[3]): C, 80.15; H, 8.3.

3,3-Diphenyl-2-ethyl-5-methyltetrahydrofuran (VI).—The procedure again was identical with that employed by Wilson.[3] After recrystallization from methanol, the product melted at 89.5–90.5°.

Anal. Calcd. for $C_{19}H_{22}O$: C, 85.67; H, 8.33. Calcd. for $C_{19}H_{20}O$ (III): C, 86.32; H, 7.63. Found: C, 85.39; H, 8.28. Found (Wilson[3]): C, 86.0; H, 8.0.

4,4-Diphenyl-2,5-diacetoxyheptane.—The glycol (V) was refluxed with a mixture of acetic anhydride and pyridine for two hours. The solution was poured into water and the resulting mixture was extracted with ether. The ether layer was dried over magnesium sulfate and concentrated. The residue was taken up in petroleum ether and the oil which separated upon cooling gradually solidified. After recrystallization once from methanol and water, and twice from petroleum ether, the product melted at 76–77°.

Anal. Calcd. for $C_{23}H_{28}O_4$: C, 74.98; H, 7.66. Found: C, 75.15; H, 7.60.

2,2-Diphenyl-1,4-pentanediol (VII).—A solution of 25 g. of lithium aluminum hydride in 250 ml. of anhydrous ether was prepared. Ten milliliters of this solution was added dropwise with stirring and cooling to a solution of 10.0 g. (0.04 mole) of 2,2-diphenyl-4-pentanolactone in 100 ml. of dry benzene. After five minutes, the mixture was decomposed with water. The resulting slurry was poured with stirring into a mixture of 200 ml. of ice and 25 ml. of concentrated sulfuric acid. The organic layer was washed twice with water and evaporated on the steam-bath to leave a solid, m.p. 111–113°. Recrystallization from ethanol and water gave 8.4 g. (83%) of crystals, m.p. 114.0–115.5°. A mixed m.p. with the starting lactone was depressed below 100°.

Anal. Calcd. for $C_{17}H_{20}O_2$: C, 79.65; H, 7.86. Found: C, 79.50; H, 8.03.

2,2-Diphenyl-1,4-diacetoxypentane.—Five grams of 2,2-diphenyl-1,4-pentanediol (VII) was dissolved in 20 ml. of acetic anhydride. On the addition of 3 drops of sulfuric acid the mixture spontaneously warmed to 80°. After 15 minutes on the steam-bath, the greenish mixture was poured into 300 ml. of water and stirred. After cooling the mixture, the oil solidified. A recrystallization from acetone–water (Darco) gave 4.5 g., m.p. 78–79.5° (68%).

Anal. Calcd. for $C_{21}H_{24}O_4$: C, 74.09; H, 7.11. Found: C, 74.38; H, 7.33.

Hydrolysis of this diacetate with aqueous alcoholic potassium hydroxide yielded only starting glycol, indicating that the sulfuric acid used did not cause a neopentyl-type rearrangement.

3,3-Diphenyl-5-methyltetrahydrofuran.—Prepared by the method used for compound VI (above), m.p. 46.5–48° (acetone–water).

Anal. Calcd. for $C_{17}H_{18}O$: C, 85.67; H, 7.61. Found: C, 85.69; H, 7.83.

3,3-Diphenyl-1,4-hexanediol.—Prepared by Wilson's[3] general method using ethylmagnesium bromide and 2,2-diphenyl-4-butanolactone[6]; recrystallized twice from methylcyclohexane, m.p. 130–131°.

Anal. Calcd. for $C_{18}H_{22}O_2$: C, 79.96; H, 8.20; two active hydrogen atoms, 0.75. Found: C, 80.00; H, 8.01; active hydrogen, 0.80.

3,3-Diphenyl-1,4-diacetoxyhexane.—Prepared by the method given above for the acetylation of 4,4-diphenyl-2,5-heptanediol, m.p. 95–96° (from ethanol). Sublimation at 1 mm. did not alter the melting point.

Anal. Calcd. for $C_{22}H_{26}O_4$: C, 74.57; H, 7.37. Found: C, 74.55; H, 7.58.

3,3-Diphenyl-2-ethyltetrahydrofuran.—Prepared by the method given above for the preparation of 3,3-diphenyl-2-ethyl-5-methyltetrahydrofuran, m.p. 70–71° (from methanol).

Anal. Calcd. for $C_{18}H_{20}O$: C, 85.67; H, 7.99. Found: C, 85.75, 85.60; H, 8.09, 7.95.

4,4-Diphenyl-5-methyl-2,5-hexanediol.—Methylmagnesium iodide was prepared from 9.72 g. (0.4 mole) of magnesium and 56.8 g. (0.4 mole) of methyl iodide, using a total of 125 ml. of ether. This Grignard solution was refluxed for 18 hours with a solution of 25.2 g. (0.1 mole) of 2,2-diphenyl-4-pentanolactone in 100 ml. of benzene. The reaction was worked up in the usual manner. Recrystallization of the product from methanol gave white crystals, m.p. 184.5–185.5°, 10 g. (36%).

Anal. Calcd. for $C_{19}H_{24}O_2$: C, 80.24; H, 8.51; two active hydrogen atoms, 0.70. Found: C, 80.21; H, 8.44; active hydrogen, 0.68.

4,4-Diphenyl-5-methyl-2,5-hexanediol Monoacetate.—This compound was prepared by the pyridine–acetic anhydride method described above. The acetylation is presumed to occur on the secondary alcoholic group, as the tertiary alcoholic group is sterically more hindered; m.p. 145.5–147° (from methanol and then sublimed).

Anal. Calcd. for $C_{21}H_{26}O_3$: C, 77.26; H, 8.03. Found: C, 77.15; H, 7.92.

2,2,5-Trimethyl-3,3-diphenyltetrahydrofuran.—The dehydration was carried out as reported for the preparation of 3,3-diphenyl-2-ethyl-5-methyltetrahydrofuran (VI). The product was recrystallized from methanol, m.p. 65–66.5°.

Anal. Calcd. for $C_{19}H_{22}O$: C, 85.67; H, 8.33. Found: C, 85.57; H, 8.33.

2,2-Diphenyl-4-butanolactone.—This compound was prepared by the method of Attenborrow, *et al.*, but the imidolactone was isolated by the method reported[9] for the imidolactone in the preparation of 2,2-diphenyl-4-pentanolactone. The 3,3-diphenyl-2-furanonimine melted at 80.5–81.5° (from methylcyclohexane), and a mixture of this compound with 2,2-diphenyl-4-butanolactone gave a large depression of the melting point.

Anal. Calcd. for $C_{16}H_{15}ON$: N, 5.90. Found: N, 5.76.

SPECTRAL DATA

	Ultraviolet		Infrared	
Compound	λ, mμ	E[a]	λ, μ	Assignment
V	254	403	3.10 sh.	Bonded OH groups
	260	475	3.21	
	264 sh.	420		
	270 sh.	290		
VI	255	403	No band at 3.00–3.25 m	(OH region)
	260	480	No band at 5.00–6.00 m	(C=O region)
	264	460		
	271	355		
VII	254	380	3.05	Bonded OH groups
	259	455	3.15	
	265 sh.	375		
	269	295		

[a] Molar extinction coefficient in 95% ethanol.

BETHLEHEM AND PHILADELPHIA, PENNA.

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(9) N. R. Easton, J. H. Gardner and J. R. Stevens, THIS JOURNAL, **69**, 2941 (1947).