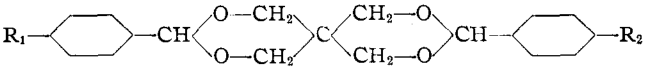
[CONTRIBUTION FROM THE WEIZMANN INSTITUTE OF SCIENCE]

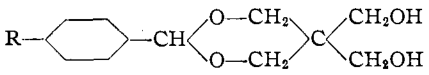
Exchange Reactions between Aldehydeacetals and Aldehydes. I

BY ELIAHU BOGRACHOV[1]

Whilst the exchange reaction between aldehydes R'CHO and aldehyde derivatives of the type RCH=NY has been known for some time, and also the reaction between acetals $RCH(OR')_2$ and alcohols R''OH has been investigated,[1a] very little appears to be known regarding the exchange between aldehyde acetals $RCH(OR')_2$ and aldehydes R''CHO. Tanasescu and Iliescu[2] have observed that the mono-(*o*-nitrobenzal) derivative of pentaerythritol, when treated with *p*-nitrobenzaldehyde in presence of sulfuric acid or phosphorus pentoxide, gives the di-(*p*-nitrobenzal) derivative of pentaerythritol. Similarly, Fairbourne and Woodley[3] reported that mono-(*p*-dimethylaminobenzal)-pentaerythritol and benzaldehyde give dibenzalpentaerythritol.

The Rumanian authors have ascribed this peculiar behavior to the presence, in their starting material, of free hydroxyl groups, as di-(*o*-nitrobenzal)-pentaerythritol was not attacked, upon treatment with *p*-nitrobenzaldehyde. This hypothesis would seem to be supported by the instability of the diacetals of dipentaerythritol, which, too, contain free methylol groups (one at each central carbon atom). Nevertheless, the hypothesis is not satisfactory. It is made untenable by the following observations: dibenzalpentaerythritol (I, $R_1 = R_2 = H$) treated in benzene solution and in the presence of a sulfonic acid with *p*-nitrobenzaldehyde is quantitatively converted into di-(*p*-nitrobenzal)-pentaerythritol (I, $R_1 = R_2 = NO_2$). In the dibenzoate and the di-(*p*-nitrobenzoate) of monobenzalpentaerythritol, (II, R = H), the benzal residue is replaced by the *p*-nitrobenzal group, on treatment with *p*-nitrobenzaldehyde. This reaction, too, is only possible in the presence of an acidic catalyst.

I 

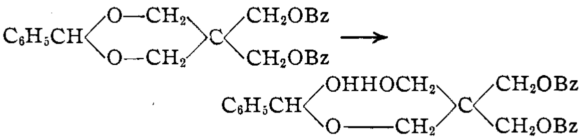
II 

The dibenzoate of mono-(*p*-nitrobenzal)-pentaerythritol was saponified by alcoholic potash solution to mono-(*p*-nitrobenzal)-pentaerythritol (II, R = NO_2). From this, hitherto unavailable mixed acetals[3] could be prepared by reaction with aldehydes which are "less reactive" than *p*-nitrobenzaldehyde. Benzaldehyde, *e. g.*, gives (*p*-nitrobenzal)-(benzal)-pentaerythritol (I, $R_1 = H, R_2 = NO_2$).

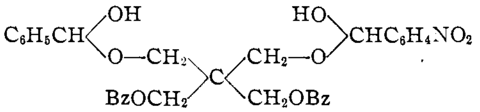
It has been observed in the course of this investigation that the method of Kraft[4] for the preparation of dibenzalpentaerythritol, which is used for the determination of pentaerythritol in mixtures with dipentaerythritol, leads to mixtures of the mono- and the dibenzal compounds[5]; their ratio appears to vary with concentration, temperature and *p*H of the medium. It has now been possible to determine the optimum conditions for the preparation of either the mono- or the dibenzal derivative of pentaerythritol, in satisfactory yields. The mono-compound can be esterified in the usual manner.[6]

Whilst *p*-nitrobenzaldehyde easily displaces benzaldehyde, anisaldehyde is without effect. It may be possible to construct a sequence of activities of the aldehydes, similar to that which has been observed by Sulzbacher, Bergmann and Pariser[7] in the reaction of the benzaldehydes with ethylene glycol. An investigation of this point, which will be supplemented by a study of the influence of various catalysts is now in progress.

One is tempted to assume, that, *e. g.*, (monobenzal)-pentaerythritol dibenzoate is hydrolyzed, under the influence of the catalyst, in a manner similar to the hydrolytic fission of ordinary acetals but intramolecularly[8]



The product of this rearrangement condenses with *p*-nitrobenzaldehyde to give a hemiacetal



This condensation can simply revert; the hemiacetal can also eliminate the benzaldehyde molecule, thus giving (*p*-nitrobenzal)-pentaerythritol dibenzoate. Both reactions will again be catalyzed by hydrogen ions, whilst—to follow

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[1] Present address: Division of Plant Protection, Ministry of Agriculture, Tel-Aviv, Israel.

[1a] Delépine, *Bull. soc. chim. France*, [3] **25**, 574 (1901); *Ann. chim.*, [7] **23**, 378 (1901).

[2] Tanasescu and Iliescu, *Bull. soc. Chim. France*, [5] **5**, 1446 (1938).

[3] Fairbourne and Woodley, *J. Chem. Soc.*, 3240 (1926).

[4] Kraft, *C. A.*, **25**, 5114 (1931).

[5] Wyler, *Ind. Eng. Chem.*, *Anal. Ed.*, **18**, 777 (1946).

[6] For another method for the preparation of the diacylmonoacetals, see Barth, U. S. Patent 2,446,257 (*C. A.*, **42**, 8210 (1948)).

[7] Sulzbacher, Bergmann and Pariser, THIS JOURNAL, **70**, 2827 (1948).

[8] For a review on the chemistry of pentaerythritol acetals, see Marrian, *Chem. Revs.*, **43**, 149 (1948).

the analogy with the acetalization of aldehydes[9,10] —the hemiacetal formation is a non-catalytic process. It remains to be seen how far this sequence of reactions is determined by the reactivity of the carbonyl group of the "new" aldehyde, the differential solubilities of the two possible reaction products and the relative concentrations of the reactants.

The experiments described in this paper were carried out under the auspices of the Scientific Department of the Israeli Ministry of Defense.

Experimental Part

1. **Monobenzalpentaerythritol (II, R = H).**—To a solution of 136 g. (1 mole) of pentaerythritol in 1000 ml. of water, 106 g. of benzaldehyde and 5 ml. of concentrated hydrochloric acid (d. 1.19) were added. The mixture was shaken for five hours and then kept for twenty-four hours. The crystals were collected, washed with water, and recrystallized from 1500 ml. of water, which was made slightly alkaline by addition of sodium carbonate. A second recrystallization from toluene (1.3 to 1.5 l.) gave 175 g. of pure benzalpentaerythritol (80%); rhombic plates, m. p. 133.5°. The substance is very slightly soluble in ether or carbon tetrachloride but dissolves readily in polar solvents, such as methanol, ethanol and acetone.

Anal. Calcd. for $C_{12}H_{16}O_4$: C, 64.3; H, 7.1. Found: C, 64.4; H, 7.1.

2. **Benzalpentaerythritol Dibenzoate.**—A solution of 11.2 g. of monobenzalpentaerythritol in 30 ml. of pyridine was treated with 15 g. of benzoyl chloride, which caused an exothermic reaction. After twenty-four hours, 100 ml. of 10% sulfuric acid was added with cooling, and the crude product filtered, washed with water and sodium carbonate solution and recrystallized from isopropyl alcohol (75 ml.) or from a mixture of acetone and methanol as glistening, long needles of m. p. 120.5°; yield 19 g. (88%).

Anal. Calcd. for $C_{26}H_{24}O_6$: C, 72.2; H, 5.5. Found: C, 72.2; H, 5.4.

3. **Benzalpentaerythritol Di-*p*-nitrobenzoate.**—To a clear solution of 11.2 g. of benzalpentaerythritol in 30 ml. of pyridine, 20 g. of powdered *p*-nitrobenzoyl chloride was gradually added. The mixture was treated as in the previous experiment. Recrystallization from acetone gave 30 g. of benzalpentaerythritol di-*p*-nitrobenzoate (yield nearly quantitative); long plates, m. p. 76°.

Anal. Calcd. for $C_{26}H_{22}O_{10}N_2$: C, 59.8; H, 4.2; N, 5.4. Found: C, 59.8; H, 4.2; N, 5.5.

It is interesting to observe that the diesters of these monoacetals are extremely stable against acid hydrolysis. Here, too, the absence of free hydroxyl groups has a marked influence on the behavior of the substances.

4. **Preparation of Pure Dibenzalpentaerythritol (I, $R_1 = R_2 = H$).**—When 6.8 g. ($^1/_{20}$ mole) of pentaerythritol was azeotropically heated with a large excess (21 g., $^1/_5$ mole) of benzaldehyde in 100 ml. of benzene, in presence of 0.5 g. of *p*-toluenesulfonic acid in the manner described by Sulzbacher, Bergmann and Pariser,[7] the theoretical amount of water (0.1 mole, 1.8 ml.) collected in the receiver within two hours. After elimination of half of the solvent, and cooling, the reaction product was filtered, washed with water, and recrystallized from butanol or carbon tetrachloride as shiny hexagonal plates of dibenzalpentaerythritol; m. p. 160°; yield quantitative.[11]

Anal. Calcd. for $C_{19}H_{20}O_4$: C, 73.0; H, 6.4. Found: C, 73.0; H, 6.8.

Mkhitaryan[12] used *p*-toluenesulfonic acid as catalyst in the preparation of *aliphatic* diacetals of pentaerythritol.

5. **Reaction of Dibenzalpentaerythritol with *p*-Nitrobenzaldehyde.**—A mixture of 3 g. of dibenzalpentaerythritol, 3.3 g. of *p*-nitrobenzaldehyde and 0.5 g. of *p*-toluenesulfonic acid was heated for five hours in 50 cc. of benzene, all materials having been thoroughly dried. Upon cooling, most of the di-(*p*-nitrobenzal)-pentaerythritol (I, $R_1 = R_2 = NO_2$) separated. (The solubility of this diacetal in benzene at room temperature is 0.36 g. per 100 cc., while that of dibenzalpentaerythritol is 6.0 g. per 100 cc.) The precipitate was filtered off; the filtrate contained free benzaldehyde. After washing with water, the product (3.8 g.) was recrystallized from glycol diacetate; m. p. 234°. It was identified by mixed m. p. with a sample prepared from *p*-nitrobenzaldehyde and pentaerythritol in the usual manner. When the same reaction was carried out, using anisaldehyde instead of *p*-nitrobenzaldehyde, the starting materials were recovered unchanged.

6. **(*p*-Nitrobenzal)-pentaerythritol Dibenzoate.**—A mixture of 8.6 g. of benzalpentaerythritol dibenzoate, 3.2 g. of *p*-nitrobenzaldehyde, 0.5 g. of α-naphthalenesulfonic acid and 35 cc. of benzene was refluxed for six hours. The color changed to a deep brown. After evaporation of a third of the solvent, the product was left for twenty-four hours at 0°, and the crystals which separated, were washed with a little methanol and water; yield 8.9 g. (93%); from toluene, clusters of needles, m. p. 153°.

Anal. Calcd. for $C_{26}H_{23}O_8N$: C, 65.4; H, 4.8. Found: C, 65.9; H, 4.9.

7. **(*p*-Nitrobenzal)-pentaerythritol (II, R = NO_2).**—A mixture of 4.75 g. of (*p*-nitrobenzal)-pentaerythritol dibenzoate, 8 ml. of 33% sodium hydroxide solution and 50 ml. of 90% alcohol was refluxed for six hours. The color changed through reddish to deep brown. Most of the alcohol was distilled off, and the residue triturated with, and recrystallized from water and from ethanol as needles, m. p. 161.5°; yield 3 g. (88%).

Anal. Calcd. for $C_{12}H_{15}O_6N$: C, 53.5; H, 5.6. Found: C, 53.4; H, 5.8.

8. **Benzal-(*p*-nitrobenzal)-pentaerythritol (I, R_1 = H, $R_2 = NO_2$).**—To a clear solution of mono (*p*-nitrobenzal)-pentaerythritol (0.5 g.) in alcohol (10 ml.), 0.5 ml. of concentrated hydrochloric acid and 1.5 ml. of a 40% alcoholic solution of benzaldehyde were added. Within several hours, crystals separated which were collected, washed with methanol and sodium carbonate solution, and recrystallized from isopropyl alcohol or glycol diethyl ether; gold-colored needles of m. p. 183°; yield almost the theoretical.

Anal. Calcd. for $C_{19}H_{19}O_6N$: C, 63.9; H, 5.3; N, 3.9. Found: C, 63.8; H, 5.3; N, 4.2.

9. **(*p*-Nitrobenzal)-pentaerythritol Di-*p*-nitrobenzoate.**—Benzalpentaerythritol di-*p*-nitrobenzoate (5.2 g.), *p*-nitrobenzaldehyde (1.5 g.) and benzene (35 ml.) was refluxed for two hours. No precipitate was formed, and no benzaldehyde odor was detected, upon concentration of a few drops of the solution. As soon as some crystals of α-naphthalenesulfonic acid (0.5 g.) were introduced, a strong reaction took place, and the solution became turbid; after ten to fifteen minutes, the flask was full of crystals. The substance was heated for another thirty minutes and the product filtered after twenty-four hours and washed with methanol and water; 5.5 g. of the desired compound was obtained; theoretical yield. Recrystallization from toluene or glycol diethyl ether gave slightly yellowish needles, m. p. 133°.

Anal. Calcd. for $C_{26}H_{21}O_{12}N_3$: N, 7.4. Found: N, 7.7.

Summary

In presence of acidic catalysts, *p*-nitrobenzaldehyde replaces the benzal residue in dibenzalpentaerythritol, and in the dibenzoate and di-(*p*-nitrobenzoate) of monobenzalpentaerythritol. From the mono-(*p*-nitrobenzal)-pentaerythritol, thus

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[9] Loebering and Fleischmann, *Ber.*, **70**, 1713 (1937).

[10] Adkins and Broderick, THIS JOURNAL, **50**, 499 (1928).

[11] Read, *J. Chem. Soc.*, **101**, 2090 (1912).

[12] Mkhitaryan, *C. A.*, **34**, 4381 (1940).

made accessible, mixed acetals can be prepared.

A mechanism for the exchange reaction has been proposed.

A procedure for the preparation of pure monobenzal- and pure dibenzalpentaerythritol is described.

DANIEL SIEFF RESEARCH INSTITUTE
REHOVOTH, ISRAEL

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[CONTRIBUTION FROM THE DEPARTMENT OF INDUSTRIAL CHEMISTRY, FACULTY OF ENGINEERING, KYÔTO UNIVERSITY]

The Preparation of Synthetic Estrogens. V.[1] New Routes to 3,3-Bis-(*p*-hydroxyphenyl)-4-hexanone and the Allied Substances

BY KEIITI SISIDO, HITOSI NOZAKI AND OSAMU KURIHARA

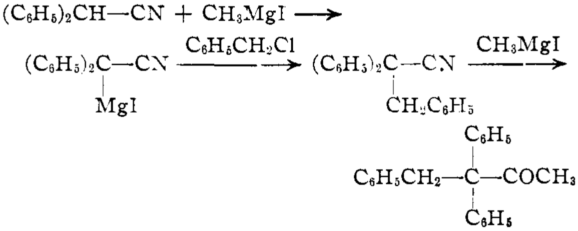
3,3-Bis-(*p*-hydroxyphenyl)-4-hexanone and its derivatives, *viz.*, ethers and esters, have been used as key intermediates in the synthesis of diethylstilbestrol.[2,3,4] In the first paper of this series[4] we described a preparation of the ketone by a pinacolone rearrangement of 3,4-di-*p*-anisyl-3,4-hexanediol as well as the succeeding conversion of the product to diethylstilbestrol. In the course of subsequent investigations we have developed new methods for the preparation of the pinacolone derivatives.

The first one consists in an adaptation of the condensation between phenol and biacetyl that we had reported in the previous paper.[1] Condensation of phenol with bipropionyl in place of biacetyl by the action of sulfuric acid resulted in the formation of the desired 3,3-bis-(*p*-hydroxyphenyl)-4-hexanone. Since the ketone formed a viscous oil, it was converted into the crystalline diacetate[2] for the identification.

It is of interest to note the structural resemblance between the pinacolone and analgesic aminoketones of the "amidone" (methadon) series. Amidone and the allied substances may be regarded as mixed pinacolones, since in these ketone derivatives two phenyl radicals and a β-amino-substituted alkyl group are attached to a quaternary carbon atom adjacent to a carbonyl group. Accordingly, methods[5] for synthesizing the analgesics may also be applicable to the preparation of estrogenic stilbestrol derivatives. This constitutes another approach to the pinacolone.

Di-*p*-anisylacetonitrile was ethylated in the presence of sodium amide and the resulting α,α-di-*p*-anisyl-*n*-butyronitrile, a new compound, was treated with ethylmagnesium bromide. Hydrolysis of the reaction product with hydrochloric acid yielded 3,3-di-*p*-anisyl-4-hexanone. In the course of this Grignard reaction, when the dianisylbutyronitrile was mixed with 5 moles of ethylmagnesium bromide and was heated at 130–170° for two and a half hours, there took place, besides the Grignard condensation, demethylation in the anisyl groups; acetylation of the resulting product gave 3,3-bis-(*p*-acetoxyphenyl)-4-hexanone, which did not depress the m. p. of the specimen obtained in the condensation of phenol with bipropionyl.

The third method for the pinacolone synthesis is a modification of this process in which a Grignard reagent is used instead of sodium amide as a condensing agent. We have discovered that treatment of a reaction mixture obtained from diphenylacetonitrile and methylmagnesium iodide with benzyl chloride, followed by heating at 60–110° during eight hours, gave 1,2,2-triphenyl-3-butanone in a 64% yield based on the diphenylacetonitrile. If this reaction was interrupted after a three-hour heating at 50–65°, α,α,β-triphenylpropionitrile was obtained in a 67% yield. Undoubtedly the first step of this reaction consists in a replacement of the active hydrogen of the diphenylacetonitrile with a halomagnesium residue of the Grignard reagent. The halomagnesium residue thus attached to the nitrile is then substituted with benzyl radical. In this reaction, when there is an excess of the Grignard reagent, it adds to the nitrile group in the usual way yielding a mixed pinacolone, 1,2,2-triphenyl-3-butanone.



$$(C_6H_5)_2CH{-}CN + CH_3MgI \longrightarrow \underset{\displaystyle MgI}{(C_6H_5)_2C{-}CN} \xrightarrow{C_6H_5CH_2Cl} \underset{\displaystyle CH_2C_6H_5}{(C_6H_5)_2C{-}CN} \xrightarrow{CH_3MgI} C_6H_5CH_2{-}\overset{\displaystyle C_6H_5}{\underset{\displaystyle C_6H_5}{C}}{-}COCH_3$$

Similar reactions of a Grignard reagent have been observed recently by Hauser, Saperstein and Shivers,[6] by Stanley and Wawzonek[7] as well as by Fuson and Porter.[8]

Unfortunately lower yields of the pinacolone derivatives were obtained in the reactions of diphenyl- and of di-*p*-anisylacetonitriles with methyl or ethyl iodide in the presence of appropriate Grignard reagents. There resulted also unalkyl

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(1) Previous paper: Sisido, Nozaki and Iwako, THIS JOURNAL, **71**, 2037 (1949).

(2) Wessely, Kerschbaum, Kleedorfer, Prillinger and Zajic, *Monatsh.*, **73**, 127 (1940).

(3) Adler, Gie and von Euler, Swedish Patent 115,816, Feb. 12, 1946; *C. A.*, **41**, 486 (1947); U. S. Patent 2,421,401, June 3, 1947.

(4) Sisido and Nozaki, THIS JOURNAL, **70**, 776 (1948).

(5) See for example: Schultz, Robb and Sprague, *ibid.*, **69**, 2454 (1947).

(6) Hauser, Saperstein and Shivers, *ibid.*, **70**, 606 (1948).

(7) Stanley and Wawzonek, *ibid.*, **68**, 1157 (1946).

(8) Fuson and Porter, *ibid.*, **70**, 895 (1948).