16. *Some Derivatives of Phloroglucinol Trimethyl Ether.*

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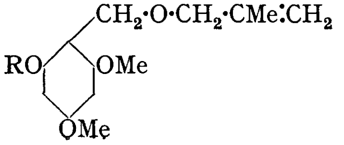
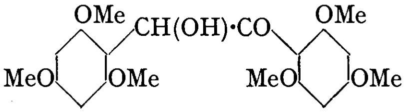
Attempts to prepare 2 : 4 : 6-trimethoxybenzyl alcohol by the reduction of the corresponding aldehyde gave what is probably 2 : 4 : 6 : 2′ : 4′ : 6′-hexamethoxybenzoin. 2 : 4 : 6-*Trimethoxybenzylamine* reacted with nitrous acid to give 2 : 4 : 6 : 2′ : 4′ : 6′-*hexamethoxydiphenylmethane,* also obtained by the interaction of phloroglucinol trimethyl ether with formaldehyde in the presence of piperidine acetate. No satisfactory process for the preparation of the required alcohol was devised.

IT was suggested recently (Penfold and Simonsen, *J. Proc. Roy. Soc., New South Wales,* 1938, **71**, 291) that the phenolic ether, bæckeol, occurring in the essential oils from various species of *Myrtaecae,* had the structure (I; R = H) and it seemed desirable to attempt the synthesis of its methyl ether (I; R = Me) by the condensation of 2 : 4 : 6-trimethoxybenzyl alcohol with 3-chloro*iso*butylene.

(I.)





(II.)

Freudenberg and Harder (*Annalen*, 1937, **451**, 222) have described the preparation of this alcohol by the hydrogenation of 2 : 4 : 6-trimethoxybenzaldehyde in the presence of a nickel–kieselguhr catalyst, 2 : 4 : 6-trimethoxytoluene being obtained if a palladium catalyst is used. We can confirm the latter observation, but have been unable to prepare the alcohol, using a number of nickel catalysts. Either the unchanged aldehyde was recovered or intractable gums were obtained (it is well known that the preparation of selective hydrogenation catalysts is not easy and we do not wish to suggest that Freudenberg and Harder's work is incorrect). In exploring other methods for the preparation of this alcohol we obtained new derivatives of phloroglucinol trimethyl ether which appear to us worthy of record.

Reduction of 2 : 4 : 6-trimethoxybenzaldehyde with zinc dust in acetic acid or acetic anhydride solution resulted in the formation of 2 : 4 : 6-trimethoxytoluene : the aldehyde was not reduced by aluminium ethoxide at room temperature. With aluminium *iso*propoxide in *iso*propyl-alcoholic solution, reduction appeared to proceed smoothly but the quantity of acetone produced, estimated in the distillate as the 2 : 4-dinitrophenylhydrazone, was much below the theoretical quantity. The product of the reaction, which was a gum, decomposed on attempted distillation under diminished pressure, but a crystalline 2 : 4-*dinitrophenylhydrazone*, m. p. 275—276°, was prepared, which analysis showed to be a derivative of 2 : 4 : 6 : 2′ : 4′ : 6′-hexamethoxybenzoin (II). This substance was obviously formed by an ordinary benzoin condensation; it is possible that a small amount of the required alcohol was formed and underwent further condensation. The aldehyde was recovered unchanged after prolonged digestion with potassium hydroxide solution.

By the catalytic hydrogenation of 2 : 4 : 6-trimethoxybenzaldoxime in acetic acid solution, a palladium–norit catalyst being used, the secondary base, 2 : 4 : 6 : 2′ : 4′ : 6′-hexamethoxydibenzylamine, m. p. 118—119°, was obtained; when, however, the reduction was carried out under the conditions used by Schales (*Ber.*, 1935, **68**, 1934), the primary base, 2 : 4 : 6-*trimethoxybenzylamine*, m. p. 59—60°, was formed in excellent yield. The nitrite of the base, prepared by the action of sodium nitrite in acetic acid solution, was stable at room temperature, but decomposed on warming with the formation of much tar. No alcohol could be isolated, the main product of the reaction being 2 : 4 : 6 : 2′ : 4′ : 6′-*hexamethoxydiphenylmethane*, m. p. 116—117°. The formation of this substance suggests that the benzyl alcohol is the primary product of the reaction and that this then condenses with a second molecule, from which the primary alcoholic group is eliminated as carbon dioxide after oxidation by the nitrous acid present. Only resins were obtained when silver nitrite was allowed to react with the hydrochloride of the base.

The marked reactivity of the phloroglucinol nucleus was further exemplified in attempts to apply the Lederer–Manasse reaction to phloroglucinol dimethyl ether, since its condensation with formaldehyde gave intractable products of high molecular weight which were not further examined. Phloroglucinol trimethyl ether, however, condensed readily with formaldehyde in the presence of piperidine acetate to give 2 : 4 : 6 : 2′ : 4′ : 6′-hexamethoxydiphenylmethane. We have been unable to find an analogy to this direct condensation of a phenolic ether with an aldehyde under these conditions.

Experimental.

2 : 4 : 6-*Trimethoxybenzylamine.*—To a suspension of palladium–norit (1 g.) in acetic acid (60 c.c.) and sulphuric acid (6 c.c.) shaken in hydrogen, a solution of 2 : 4 : 6-trimethoxybenzaldoxime (5 g.) in acetic acid (80 c.c.) was added during 8 hours. The filtered solution was basified with aqueous soldium hydroxide (NaOH, 140 g.) and the solid which separated was extracted with ether. The *base*, remaining after the removal of the ether from the dried extract, had b. p. 165°/12 mm. and crystallised in the receiver. It separated from ligroin (b. p. 60—80°) in somewhat hygroscopic needles, m. p. 59—60° (Found : C, 61·2; H, 7·3; N, 7·3. $C_{10}H_{15}O_3N$ requires C, 60·9; H, 7·6; N, 7·1%). The *hydrochloride* crystallised from dilute hydrochloric acid in hygroscopic rosettes of needles, m. p. 92° (Found : N, 3·8; Cl, 10·0. $C_{10}H_{15}O_3N,HCl,7H_2O$ requires N, 3·9; Cl, 9·9%). The *acetyl* derivative crystallised from methyl alcohol in fine needles, m. p. 153—154° (Found : C, 59·9; H, 7·1. $C_{12}H_{17}O_4N$ requires C, 60·2; H, 7·1%).

After distillation of the base a small high-boiling residue remained; this consisted of the secondary amine. It was obtained as the main product when the oxime (9·2 g.) in acetic acid (100 c.c.) was shaken with hydrogen in the presence of palladium–norit for 16 hours. 2 : 4 : 6 : 2′ : 4 : 6′-*Hexamethoxydibenzylamine* crystallised from ether–benzene in large cubes, m. p. 118—119° (Found : C, 63·9; H, 7·5. $C_{20}H_{27}O_6N$ requires C, 63·7; H, 7·2%).

2 : 4 : 6 : 2′ : 4′ : 6′-*Hexamethoxydiphenylmethane*.—(i) To a solution of the primary base (4·2 g.) in acetic acid (2·1 g.) and water (20 c.c.), a concentrated aqueous solution of sodium nitrite (1·6 g.) was slowly added. The evolution of gas was slight at room temperature, although the solution clouded slightly, but was vigorous on the water-bath and a brown oil separated. After 1 hour aqueous sodium hydroxide (NaOH, 5 g.) was added, and the solution boiled for 15 minutes. The cooled alkaline solution was extracted with ether, which left much tar undissolved; evaporation of the dried extract yielded a viscid yellow oil (2·5 g.), which crystallised on trituration with a little ether. The *diphenylmethane* crystallised from ether–benzene in long needles, m. p. 116—117°, unchanged by further crystallisation [Found : C, 65·3; H, 6·7; OMe, 51·1. $C_{13}H_6(OMe)_6$ requires C, 65·5; H, 6·9; OMe, 53·4%]. Acidification of the alkaline solution gave a crystalline solid (0·4 g.), decomp. 127°, which decomposed with evolution of nitrous fumes on attempted crystallisation.

(ii) *Condensation of phloroglucinol trimethyl ether and formaldehyde.* To a solution of the trimethyl ether (1 g.) and formalin solution (40%; 1 g.) in alcohol, a few drops of piperidine acetate were added and the mixture was heated on the water-bath for 3 hours. After the addition of water the precipitated oil was dissolved in ether, and the ethereal extract washed with dilute sulphuric acid and aqueous sodium carbonate; after removal of the ether the oil was distilled in steam to remove the unchanged trimethyl ether (0·1 g.). The non-volatile residue (0·8 g.) was shaken with ether, which left undissolved an amorphous solid (0·3 g.); evaporation of the ethereal extract gave an oil (0·4 g.), which crystallised on trituration with ligroin. After recrystallisation from ligroin (b. p. 60—80°) or ether–benzene 2 : 4 : 6 : 2′ : 4′ : 6′-hexamethoxydiphenylmethane was obtained, m. p. 116—117° alone and in admixture with the substance described above.

Reduction of 2 : 4 : 6-*Trimethoxybenzaldehyde with Aluminium* iso*Propoxide*.—A mixture of the aldehyde (5 g.), aluminium *iso*propoxide (4 g.), and *iso*propyl alcohol (50 c.c.) was distilled, the volume of the liquid being kept constant by addition of *iso*propyl alcohol, until acetone could no longer be detected in the distillate. After removal of the *iso*propyl alcohol in steam the residual oil was dissolved in ether, and the ethereal extract washed with sodium bisulphite solution to remove unchanged aldehyde and then with aqueous sodium carbonate before drying. Evaporation of the solvent gave a viscid gum (4·5 g.). This was converted into the 2 : 4-*dinitrophenylhydrazone*, which crystallised from *cyclo*hexyl acetate in bright red needles, m. p. 270°, raised to 275—276° by further crystallisation (Found : C, 54·7; H, 4·8. $C_{26}H_{28}O_{11}N_4$ requires C, 54·5; H, 4·9%).

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