methoxybenzoic acid yielded 20.4 g. (94.2%) 3,4,5-trimethoxybenzoyl chloride, m.p. 79–80°, lit. 76–78.[13]

Methyl 3-acetoxy-5-piperidinomethylbenzoate hydrochloride (Ia). To a mixture of 7.0 g. (0.025 mol.) of methyl 3-hydroxy-5-piperidinomethylbenzoate hydrochloride and 150 ml. of pyridine contained in a 250-ml. glass-stoppered flask was added 15 ml. of acetic anhydride. The mixture after shaking for 3 hr. yielded a homogeneous solution which was allowed to stand overnight at room temperature. The pyridine was removed by distillation under reduced pressure and the residue dissolved in methanol. Anhydrous ether was added to the methanol solution until a faint turbidity was produced. The product then crystallized upon cooling, to yield 6.3 g. (78%) of methyl 3-acetoxy-5-piperidinomethylbenzoate hydrochloride, m.p. 177–178°.

Anal. Calcd. for $C_{16}H_{22}O_4NCl$: C, 58.62; H, 6.77; Cl, 10.82. Found: C, 58.47; H, 6.72; Cl, 10.92.

Methyl 3-benzoyloxy-5-diethylaminomethylbenzoate hydrochloride (Ib). Five g. (0.018 mol.) of methyl 3-hydroxy-5-diethylaminomethylbenzoate hydrochloride, 150 ml. of pyridine and 5 ml. of benzoyl chloride were placed in a glass-stoppered flask, shaken for 30 min. and allowed to stand for 24 hr. at room temperature. After removal of the pyridine under pressure, the residue was dissolved in isopropyl alcohol and anhydrous ether was added to produce a faint turbidity. Upon cooling, the product crystallized and 4.7 g. (68%) of methyl 3-benzoyloxy-5-diethylaminomethylbenzoate hydrochloride was obtained, m.p. 167–168° (dec.).

Anal. Calcd. for $C_{20}H_{24}O_4NCl$: C, 63.58; H, 6.40; Cl, 9.39. Found: C, 63.28; H, 6.13; Cl, 9.50.

Methyl 3-(3′,4′,5′-trimethoxybenzoyloxy-5-piperidinomethylbenzoate hydrochloride) (Ic). A mixture of 5.0 g. (0.018 mol.) of methyl 3-hydroxy-5-piperidinomethylbenzoate hydrochloride, 8.1 g. (0.036 mol.) of 3,4,5-trimethoxybenzoyl chloride and 250 ml. of pyridine was shaken for 4 hr. The homogeneous solution was then allowed to stand at room temperature for one day. Upon the removal of the pyridine under reduced pressure, a red solid was obtained. After recrystallization of the solid from methanol and ether, 6.3 g. (75%) of colorless methyl 3-(3′,4′,5′-trimethoxybenzoyloxy)-5-piperidinomethylbenzoate hydrochloride was obtained, m.p. 202–203° (dec.).

Anal. Calcd. for $C_{24}H_{30}O_7NCl$: C, 60.05; H, 6.30; Cl, 7.39. Found: C, 59.80; H, 6.21; Cl, 7.34.

Methyl 3-(3′,4′,5′-trimethoxybenzoyloxy-5-diethylaminobenzoate hydrochloride) (Id). From 5.0 g. (0.018 mol.) of methyl 3-hydroxy-5-diethylaminomethylbenzoate hydrochloride, 8.5 g. (0.036 mol.) of 3,4,5-trimethoxybenzoyl chloride, and 250 ml. of pyridine, 4.95 g. (58%) of methyl 3-(3′,4′,5′-trimethoxybenzoxy)-5-diethylaminomethylbenzoate hydrochloride was obtained when the procedure described for the preparation of methyl 3-(3′,4′,5′-trimethoxybenzoyloxy-5-piperidinomethylbenzoate hydrochloride) was followed, m.p. 191–192°.

Anal. Calcd. for $C_{23}H_{30}O_7NCl$: C, 59.04; H, 6.46; Cl, 7.58. Found: C, 59.34; H, 6.42; Cl, 7.48.

3′-Piperidinomethylphenyl 3,4,5-trimethoxybenzoate hydrochloride (IIIc). A solution of 6.1 g. (0.026 mol.) of 3,4,5-trimethoxybenzoyl chloride in 50 ml. of ether was added to a solution of 3.0 g. (0.013 mol.) of 3-piperidinomethylphenol hydrochloride in 25 ml. of 10% sodium hydroxide and the mixture was vigorously shaken for 20 min. The ether layer was separated and the aqueous layer was extracted with two 25-ml. portions of ether which were combined with the original ether solution. The combined ether extract was washed with 20 ml. of water and dried over anhydrous magnesium sulfate. Anhydrous hydrogen chloride when passed through the ether solution produced a white solid. After recrystallization of the solid from methanol and ether, 3.5 g. (53%) of 3′-piperidinomethylphenyl 3,4,5-trimethoxybenzoate hydrochloride was obtained, m.p. 163–164°. A mixed melting point with the starting hydroxyl compound showed a marked depression (142–147°).

Anal. Calcd. for $C_{22}H_{23}O_5NCl$: C, 62.63; H, 6.69; Cl, 8.40. Found: C, 62.74; H, 6.60; Cl, 8.32.

3′-Diethylaminomethylphenyl 3,4,5-trimethoxybenzoate hydrochloride (IIId). From 2.0 g. (0.009 mol.) of 3-diethylaminomethylphenol hydrochloride, and 4.3 g. (0.018 mol.) of 3,4,5-trimethoxybenzoyl chloride, 3.0 g. (79%) of 3′-diethylaminomethylphenyl 3,4,5-trimethoxybenzoate hydrochloride was prepared in a manner analogous to that described for 3′-piperidinomethylphenyl 3,4,5-trimethoxybenzoate hydrochloride, m.p. 166–167°.

Anal. Calcd. for $C_{21}H_{28}O_5NCl$: C, 61.53; H, 6.89; Cl, 8.65. Found: C, 61.47; H, 7.29; Cl, 8.77.

Acknowledgment. The authors are grateful to Abbott Laboratories for screening the compounds for pharmacological activity.

CHICAGO, ILL.

(13) J. Koo, *J. Am. Chem. Soc.*, **75**, 720 (1953).

[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

Some Acetate Migration and Participation Reactions in Steroids[1]

ROBERT G. SCHULTZ[2]

Received June 29, 1959

In an attempt to produce cholestan-3α,5α-diol-6-one-3,5-diacetate by solvolysis of cholestan-3β,5α-diol-6-one-3-tosylate-5-acetate in dimethylformamide, water, and potassium acetate, cholestan-3α,5α-diol-6-one-3-acetate was the only product isolated. When the reaction was carried out without added potassium acetate the product was cholestan-3α,5α-diol-6-one-5-acetate. The 5-acetate rearranged to the 3-acetate by treatment with dimethylformamide, water, and potassium acetate.

In the course of other synthetic studies, it became necessary to synthesize cholestan-3α,5α-diol-6-one diacetate (I). The route selected involved as a last step solvolysis of cholestan-3β,5α-diol-6-one-3-tosylate-5-acetate (II) with potassium acetate in a dimethylformamide-water system. The tosylate (II) was synthesized as shown.

Cholesterol (III) was oxidized to cholestan-3β,5α-diol-6-one (V) in a two-step procedure described by

(1) Presented in part at the 135th Meeting of the American Chemical Society, Boston, April 1959; Abstracts p. 23-O.

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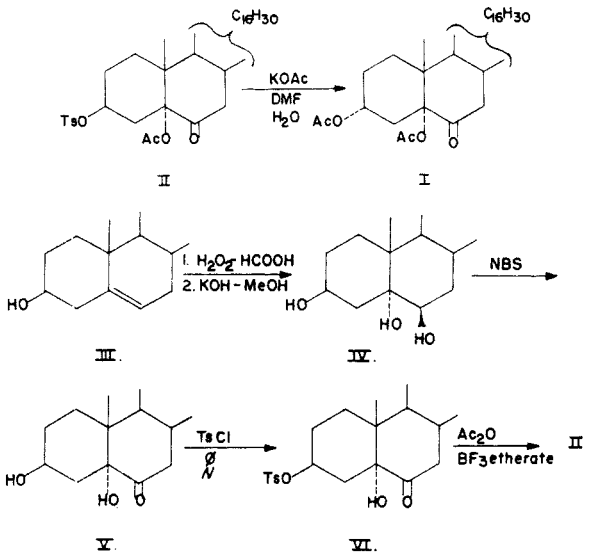
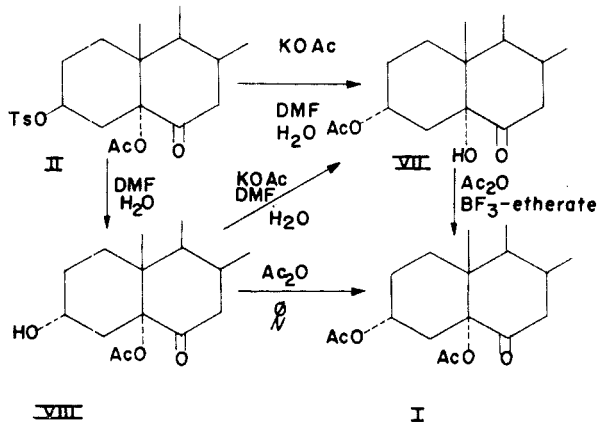


Fieser and Rajagopalan[3] and the diolone (V) was then treated successively with *p*-toluenesulfonyl chloride in pyridine and acetic anhydride with boron trifluoride–etherate catalyst to give the desired cholestan-3β,5α-diol-6-one-3-tosylate-5-acetate (II).

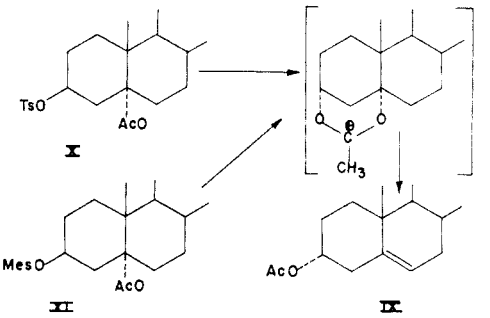
Solvolysis of II in dimethylformamide-water with added potassium acetate afforded a material which proved to be cholestan-3α,5α-diol-6-one-3-acetate (VII). Its structure was established by elemental analysis and acetylation to the desired diacetate (I) with acetic anhydride and boron trifluoride–etherate catalyst. On attempted acetylation with pyridine catalyst, only starting material (VII) was recovered.

In contrast, solvolysis of II in dimethylformamide-water *without* added potassium acetate afforded cholestan-3α,5α-diol-6-one-5-acetate (VIII). This compound could be converted to the diacetate (I) by acetylation with pyridine catalyst and rearranged to cholestan-3α,5α-diol-6-one-3-acetate (VII) on treatment with potassium acetate in a dimethylformamide-water system.

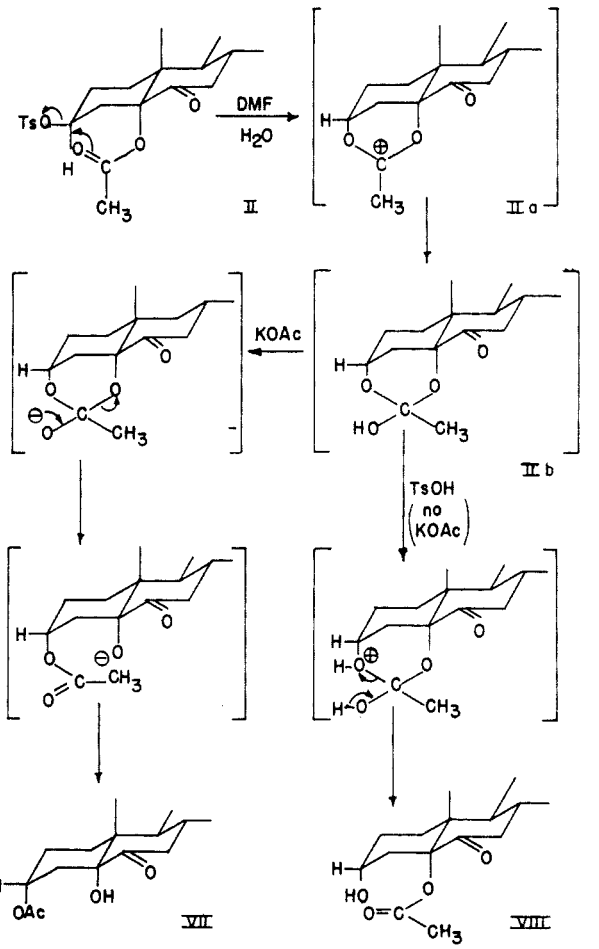


(3) L. F. Fieser and S. Rajagopolan, *J. Am. Chem. Soc.*, **71**, 3938 (1949).

A somewhat similar internal 1,3-acetate rearrangement was noted by Plattner, who obtained epicholesterol (IX) by solvolysis of either cholestan-3β,5α-diol-3-tosylate-5-acetate (X)[4a] or cholestan-3β,5α-diol-3-mesylate-5-acetate (XI).[4b] He postulated a 3,5-bridged intermediate.



A possible explanation for the rearrangements in the cholestan-diolone series involves the cyclic ortho ester structure (IIb). When potassium acetate is present, it may, in addition to acting as a buffer for the *p*-toluenesulfonic acid formed, also act as a base to remove the proton from the hydroxyl of the ortho ester. The anion so formed could then col-



(4) (a) P. A. Plattner and W. Lang, *Helv. Chim. Acta*, **27**, 1872 (1944). (b) P. A. Plattner, A. Furst, F. Koller, and W. Lang, *Helv. Chim. Acta*, **31**, 1455 (1948).

lapse to an acetate and the alkoxide of greater stability, which in this case by electrostatic considerations would be the one alpha to the carbonyl group. This alkoxide would then form cholestan-3α,5α-diol-6-one-3-acetate (VII).

In the absence of acetate buffer, the *p*-toluenesulfonic acid formed in the displacement is free to protonate one of the oxygens of the ortho ester, probably the one attached to carbon-3, since this oxygen has a greater electron density than the one attached to carbon-5. This would then account for the formation of cholestan-3α,5α-diol-6-one-5-acetate (VIII).

EXPERIMENTAL

All melting points are corrected. Microanalyses by Mr. J. Nemeth and associates.

Cholestan-3β,5α-diol-6-one (V). The procedure used was a modification of that of Fieser and Rajagopolan.[3] A suspension of 40.0 g. of cholesterol in 400 ml. of 88% formic acid was heated on a steam bath until all the solid disappeared and an oil formed. The mixture was allowed to cool to room temperature, the lumpy mass was broken up, and 40 ml. of 30% hydrogen peroxide was added. The mixture was kept at room temperature with occasional stirring for 5.5 hr. Boiling water (600 ml.) was then added and the suspension was cooled to room temperature. The solid (cholestan-3β,5α,6β-triol-3,6-diformate) was filtered, washed with water, partially air-dried, and dissolved in 1200 ml. of methanol, and 40 ml. of 25% potassium hydroxide was added. The solution was heated on the steam bath for 10 min., acidified with hydrochloric acid, diluted with 400 ml. water, and the resulting suspension was cooled and filtered. The crude cholestan-3β,5α,6β-triol, m.p. 226–232°, was washed with water and air-dried.

The crude triol was suspended in a mixture of 1 l. of ether, 150 ml. of methanol, and 150 ml. of water in a separatory funnel, and 19.6 g. of *N*-bromosuccinimide was added. The mixture was shaken until solution was complete. During this time the reaction mixture turned orange. One l. of water was added to precipitate the diolone. The ether suspension of the crystalline diolone was washed with a dilute solution of sodium bisulfite for decolorization, with sodium hydroxide solution and twice with water. The crystals were then filtered, washed with ether and air-dried, yielding 41.2 g. (95%) of cholestan-3β,5α-diol-6-one, m.p. 220–225° crude (lit. m.p. 232–233°). This material could be recrystallized from chloroform to give pure diolone, m.p. 229–231°, $[\alpha]_D^{27}$ −31.9°, M_D −133°.

Cholestan-3β,5α-diol-6-one-3-tosylate (VI). To a solution of cholestan-3β,5α-diol-6-one (15 g.) in a minimum amount (50 ml.) of dry pyridine, 11.5 g. of *p*-toluenesulfonyl chloride was added and the solution allowed to stand at room temperature for 2 days. The solution was then poured into ice and concentrated hydrochloric acid and the solid extracted with ether. The ether solution was washed with water, 5% hydrochloric acid, water, dilute potassium bicarbonate, and water. Ethanol was then added, the ether was evaporated, and crystallization from ethanol water-yielded 18.0 g. (87.8%) of cholestan-3β, 5α-diol-6-one-3-tosylate, m.p. 139–140° (dec.). Crystallization several times from ethanol-water gave pure tosylate, m.p. 135.5–136.5°, $[\alpha]_D^{27}$ −48.4°, M_D −273°, infrared bands at 3500, 1713, 1194, 1180 cm.$^{-1}$ in chloroform.

Anal. Calcd. for $C_{34}H_{52}O_5S$: C, 71.29; H, 9.15. Found: C, 71.50; H, 9.16.

This compound has been previously reported[5] and the melting point recorded as 161–163° when recrystallized from acetone-hexane. The lower melting form on recrystallization twice from acetone-hexane gave the higher melting form.

Cholestan-3β,5α-diol-6-one-3-tosylate-5-acetate (II). Cholestan-3β,5α-diol-6-one-3-tosylate (18.0 g.) was suspended in 150 ml. of acetic anhydride, 1 ml. of boron trifluoride–etherate complex was added, and the suspension was heated on a steam bath until solution occurred (about 5 min.). After the solution had cooled to room temperature, the crystals that formed were filtered, washed with acetic acid and acetic acid–water and air-dried, yielding 14.4 g. (74.2%) of cholestan-3β,5α-diol-6-one-3-tosylate-5-acetate, m.p. 147.5–149° (dec.). The filtrate on addition of water afforded additional solid, which was filtered, washed with water, and recrystallized from ethanol-water, yielding 1.95 g. of product, m.p. 145–146° (dec.). The total yield was 16.3 g. (84.5%). A sample was recrystallized from methylene chloride–hexane three times to give pure cholestan-3β,5α-diol-6-one-3-tosylate-5-acetate, m.p. 146.5–147°, $[\alpha]_D^{27}$ 3.6°, M_D 22.2°, infrared bands at 1742, 1723, 1238, 1195, 1182 cm.$^{-1}$ in chloroform.

Anal. Calcd. for $C_{36}H_{54}O_6S$: C, 70.32; H, 8.85. Found: C, 70.40; H, 8.86.

Cholestan-3α,5α-diol-6-one-3-acetate (VII). (a) *From Cholestan-3β,5α-diol-6-one-3-tosylate-5-acetate* (II). Cholestan-3β, 5α-diol-6-one-3-tosylate-5-acetate (1.23 g.) was dissolved in 25 ml. of dimethylformamide and 2 ml. of water, 2 g. of potassium acetate was added, and the solution was heated on a steam bath for 16 hr. Water was added, the suspension was cooled and the resulting solid was filtered, washed with water, air-dried, and recrystallized from ethanol-water, to yield 0.675 g. (73.4%) of cholestan-3α,5α-diol-6-one-3-acetate, m.p. 142–147°. An analytical sample, recrystallized three times from ethanol-water, had m.p. 155–156°, and infrared bands at 3580, 1743, 1723 cm.$^{-1}$ in chloroform.

Anal. Calcd. for $C_{29}H_{48}O_4$: C, 75.60; H, 10.50. Found: C, 75.45; H, 10.55.

(b) *From Cholestan-3α,5α-diol-6-one-5-acetate* (VIII). A solution containing cholestan-3α,5α-diol-6-one-5-acetate (100 mg.) and potassium acetate (200 mg.) in 6 ml. of dimethylformamide and 1 ml. of water was heated on a steam bath for 17 hr. Water was added, the suspension was cooled, and the resulting solid was filtered, washed with water, and air-dried to yield 73 mg. of crude solid, m.p. 120–122°. This solid was chromatographed on 1.5 g. of Florisil. The material eluted by 6:1 hexane-benzene was combined (crude wt. 45 mg.) and crystallized from ethanol-water, yielding 41.5 mg. (41.5%) of cholestan-3α,5α-diol-6-one-3-acetate, m.p. 156–157°. Mixed melting point with that prepared by method (a) is undepressed.

Cholestan-3α,5α-diol-6-one-5-acetate (VIII). Cholestan-3β, 5α-diol-6-one-3-tosylate-5-acetate (615 mg.) was dissolved 15 ml. of dimethylformamide and 2 ml. of water and heated on a steam bath for 16 hr. Water was added, the suspension was cooled, and the resulting solid was filtered, washed with water, and air-dried, to yield 467 mg. of solid material, m.p. 137–141°. Recrystallization of this solid from ethanol water yielded 430 mg. (93.5%) of cholestan-3α,5α-diol-6-one-5-acetate, m.p. 137–140°, infrared bands at 3500, 1735, 1721 cm.$^{-1}$ in carbon disulfide.

Cholestan-3α,5α-diol-6-one-3,5-diacetate (I) (a) *from Cholestan-3α,5α-diol-6-one-3-acetate* (VII). Cholestan-3α,5α-diol-6-one-3-acetate (30 mg.) suspended in 15 ml. of acetic anhydride and 10 drops of boron trifluoride–etherate complex was heated on a steam bath for 5 min. and then allowed to cool to room temperature and to stand for 2 hr. Water was added to decompose excess acetic anhydride and precipitate the diacetate. The suspension was cooled, filtered, washed with water and air-dried, yielding 29.5 mg. (90.2%) of cholestan-3α,5α-diol-6-one-3,5-diacetate, m.p. 186.5–187°, infrared bands at 1743, shoulder at 1728, 1268, and 1255 cm.$^{-1}$ in carbon tetrachloride. Three recrystallizations from ethanol-water yielded pure diacetate, m.p. 187–188°.

(5) H. Reich, F. E. Walker, and R. W. Collins, *J. Org. Chem.*, **16**, 1753 (1951).

Anal. Calcd. for $C_{31}H_{50}O_5$: C, 74.06; H, 10.02. Found: C, 74.03; H, 9.94.

(b) *From Cholestan-3α,5α-diol-6-one-5-acetate* (VIII). Cholestan-3α,5α-diol-6-one-5-acetate (50 mg.) was dissolved in 10 ml. of acetic anhydride and 3 ml. of pyridine and allowed to stand at room temperature for 18 hr. Water was then added, the suspension cooled, and the resulting solid was filtered, washed with water, air-dried, and recrystallized from ethanol-water, yielding 39 mg. (71.5%) of cholestan-3α,5α-diol-6-one-3,5-diacetate, m.p. 180–182°. Recrystallization from ethanol-water gave pure diacetate, m.p. 186–187°, mixed m.p. undepressed with that prepared in (a) above.

URBANA, ILL.

[CONTRIBUTION FROM THE SUMMIT RESEARCH LABORATORIES, CELANESE CORP. OF AMERICA]

Some 3,9-Dicarboxylic Acids of 2,4,8,10-Tetroxaspiro[5.5]undecane

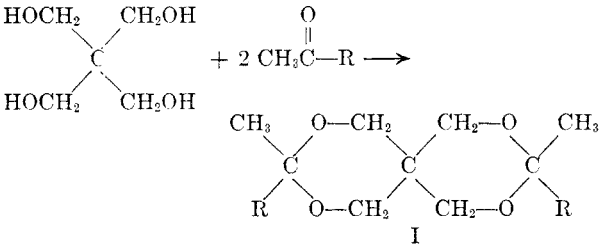
JOHN B. CLEMENTS AND LEONARD M. RICE[1]

Received July 1, 1959

A series of 3,9-disubstituted 2,4,8,10-tetroxaspiro[5.5]undecanes has been prepared by the condensation of pentaerythritol with aldehydes and acetals which contain other functions such as nitrile or ester groups. Hydrolysis of the derived nitriles and esters has led to a variety of 3,9-dicarboxylic acids. Attempts to prepare the desired acids by replacement of the halogens of 3,9-bis(halomethyl)-2,4,8,10-tetroxaspiro[5.5]undecane with appropriate nucleophiles were unsuccessful because of the extreme inertness of the halide. Finally, a very convenient method for removing dipentaerythritol from commercial pentaerythritol has been developed.

In connection with another project, it was necessary to prepare a series of 3,9-dibasic acids of 2,4,8,10-tetroxaspiro[5.5] undecane upon which we would like to report at this time. These spiro acids were prepared from pentaerythritol and a suitable aldehyde or its corresponding acetal.

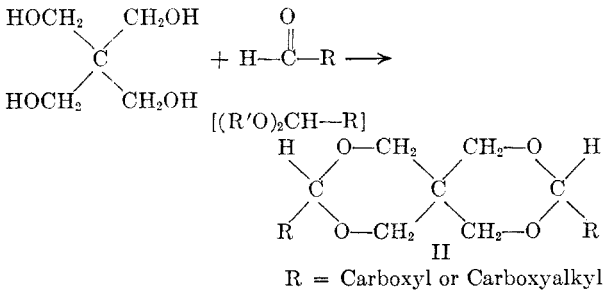
Some 30 years ago, Boeseken and Felix[2] condensed pentaerythritol with various keto esters to obtain a series of diesters (I).



I

In all of these products, positions 3 and 9 were substituted with a methyl group in addition to the fatty acid ester residue, R.

For the purpose of our investigation we were interested in the spiro acids where the 3,9 positions were not substituted by alkyl and possessed only a carboxyl or carboxyalkyl group. We took advantage in our syntheses of the condensation of pentaerythritol with aldehydes or acetals as shown in the following figure:



II

R = Carboxyl or Carboxyalkyl

The preparation of the 3,9-disubstituted 2,4,8,10-tetroxaspiro[5.5]undecanes (II) was realized by condensing pentaerythritol with a variety of aldehydes and acetals which also had an ester or nitrile function in their molecule. Thus, pentaerythritol was condensed with methyl dimethoxyacetate, ethyl 2,2-diethoxypropionate, 1,1-diethoxy-3-cyanopropane, 1,1-dimethyl-3-cyanobutyraldehyde, and 1,1-diethyl-3-cyanobutyraldehyde to give the corresponding diester or dinitrile, all in good yields. Each diester or dinitrile was hydrolyzed to the corresponding diacid. The various diesters, dinitriles, and dicarboxylic acids are listed in Table I together with pertinent data.

The condensation of methyl dimethoxyacetate with pentaerythritol to give ester V and its hydrolysis to acid VI is worthy of special note. Even though the conditions for carrying out the condensation are rather drastic, *i.e.*, 3 hr. reflux with concentrated hydrochloric acid, the ester itself is somewhat water sensitive. Thus, the diester is hydrolyzed completely to the diacid by short reflux with water alone and this was the most convenient method of preparation of the diacid. Except for this water sensitivity, the ester is not otherwise labile and remains unchanged at ordinary room conditions using no special precautions.

In all of the other condensations a small amount of *p*-toluene sulfonic acid was used as a catalyst. For the condensation of the acetals with pentaerythritol the reactants were refluxed until homogeneous and for the aldehydes the reactions were performed in refluxing toluene using a Dean-Stark trap for removal of the water as it formed. Dinitriles XI and XIII were hydrolyzed with potassium hydrox-

(1) Present address: Wyeth Laboratories, Radnor, Pa.

(2) J. Boeseken and B. B. C. Felix, *Ber.*, 61B, 787 and 1855 (1928).