min., kept for 1 hr. at 27°, and evaporated. The crystalline residue (imino ether hydrochloride) was dissolved in 20 ml. of methanol, treated with 0.10 g. of sodium borohydride in 1 ml. of water, and kept for 1 hr. at 27°. The mixture was diluted with water, and the resulting precipitate was filtered and recrystallized from methanol to give a nearly quantitative yield of colorless crystals: m.p. 248–250°; $[\alpha]^{28}D$ +53° (*c* 1, $CHCl_3$); λ_{max}^{KBr} 3.0, 5.7, 5.8 μ.

Anal. Calcd. for $C_{34}H_{48}O_5$: C, 76.08; H, 9.01. Found: C, 75.98; H, 9.02.

3β,5β,6β-Trihydroxycholestan-19-oic Acid 6,19-Lactone (XXIII).—A solution of 0.10 g. of the crude imino ether hydrochloride described in the preparation of XXIII was prepared in 5% methanolic potassium hydroxide solution and kept for 2 hr. at 27°. It was diluted with water and the resulting precipitate was collected and recrystallized from ethyl acetate to give colorless plates: m.p. 263–264°; λ_{max}^{KBr} 3.00, 3.1–3.2, 5.7 μ; $[\alpha]^{28}D$ +23° (*c* 0.30, $CHCl_3$).

Anal. Calcd. for $C_{27}H_{44}O_4$: C, 74.96; H, 10.25. Found: C, 75.12; H, 10.22.

The Constitution of a Galactomannan from the Seed of *Gleditsia amorphoides*[1]

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A galactomannan composed of 28.6% D-galactose and 71.4% D-mannose was isolated in 30% yield from the seeds of *Gleditsia amorphoides*. Periodate oxidation showed that all the mannose and galactose units were attacked since hydrolysis of the reduced oxopolysaccharide gave only glycerol (1 mole) and erythritol (2.7 moles). The periodate consumption was 4.8 moles for every four hexose residues and at the same time 1 mole of formic acid was produced. Hydrolysis of the methylated polysaccharide yielded 2,3,4,6-tetra-O-methyl-D-galactose (1 mole), 2,3,6-tri-O-methyl-D-mannose (2.1 moles), and 2,3-di-O-methyl-D-mannose (1.1 moles).

Gleditsia amorphoides is a leguminous tree that grows in the northern part of the Argentine Republic where it is known as "espina corona". Its fruit has been studied by Riqué and Pardo[2a] who showed that its composition was similar to that of locust bean fruit.[2a] As the industrial applications of the galactomannan contained in its seed are continually increasing in this country it was of interest to study whether its structure is similar to those of the already known galactomannans.

The polysaccharide was extracted from the dry and coarsely ground seed with hot water. Addition of ethanol to the aqueous extract precipitated the polysaccharide (yield 30%) as a fibrous material. This crude product was purified by fractional precipitation from its aqueous solution by increasing the concentration of ethanol stepwise; nearly 90% of the initial weight precipitated at an ethanol concentration between 22 and 26% (wt. of ethanol/wt. of solution), no significant precipitation was obtained at lower or higher concentration (upper limit 50%). After two reprecipitations the polysaccharide showed a nitrogen content of less than 0.4% and a rotatory power of $[\alpha]^{25}D$ +22.4° (water).

Evidence of its homogeneity was provided by (a) a single, sharp peak in the sedimentation pattern obtained with the ultracentrifuge, (b) its precipitation from aqueous solution over a narrow concentration range of ethanol, and (c) the fact that the product obtained after purification through its acetate[2b] displays the same physical properties as the product purified by precipitation with ethanol.

The infrared spectrum of the polysaccharide showed absorption bands at 817 and 874 $cm.^{-1}$ thus indicating the presence of α-linked D-galactopyranose units and β-linked D-mannopyranose units, respectively.[3]

Acid hydrolysis of the purified galactomannan which had a D.P. (degree of polymerization) of 116 determined chemically[4] was shown to give rise to D-galactose (28.6%) and D-mannose (71.4%) in a molar ratio of 1:2.7. Variable results were obtained in periodate oxidation studies. With 0.01 *N* periodate, 4 moles of periodate were consumed for every four hexose units and hydrolysis of the corresponding reduced oxopolysaccharide gave rise to 1 mole of mannose for every four hexose units as well as glycerol and erythritol and trace amounts of galactose. However, when the oxidation was carried out with 0.1 *N* periodate, 4.8 moles of the oxidant were consumed for every four hexose residues and hydrolysis of the corresponding polyalcohol in this case gave glycerol (1 mole) and erythritol (2.7 moles)[4,5] with only trace amounts of galactose and mannose.

This resistance of some mannose residues to the periodate oxidation has been observed in several cases (guar[6,7] and fenugreek,[8] galactomannans of Lucerne and Clover seeds[9]) and has been attributed[9] to a steric effect resulting from the highly ramified structure of the galactomannan in which mannose units form the branching points. Present knowledge, however, indicates that this phenomenon is most likely due to cyclic acetal formation.

The fact that only traces of mannose and galactose survived the periodate treatment indicate that no significant amounts of (1 → 3) linkage are present. The large proportion of erythritol released upon acid hydrolysis of the polyalcohol serves as evidence that the main polymeric linkage was of the (1 → 4) type and the ratio of this erythritol to the glycerol indicated a branching point, on the average, every three units in the backbone. The molar proportion of periodate consumed and of formic acid produced (1 mole/every four hexose units) corroborate these findings.

(1) This work was supported in part by a grant from the Consejo Nacional de Investigaciones Científicas y Técnicas.

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Hydrolysis of the methylated galactomannan yielded 2,3,4,6-tetra-O-methyl-D-galactose, 2,3-di-O-methyl-D-mannose, and 2,3,6-tri-O-methyl-D-mannose which were separated by column chromatography and identified in the usual way. Some evidences were obtained of the presence of trace amounts of a trimethylated galactose derivative that by its chromatographic behavior[10,11] could be 2,3,4-tri-O-methyl-D-galactose. It is possible that this product could form part of a small number of side chains of D-galactopyranose linked to D-galactopyranose residues by (1 → 6) linkages.

From the above results and by analogy with the structures of other galactomannans,[12] it is postulated that the galactomannan of *Gleditsia amorphoides* consists of a linear chain of (1 → 4) β-linked D-mannopyranose units, and to position 6 of one out of every three mannose units is attached by an α (1 → 6) linkage, a D-galactopyranose unit, a formulation in agreement with the specific rotations of the polysaccharide, and its methylated derivative as compared with other closely related galactomannans of known structure.[12] It is of interest to note that the general structural features of this new galactomannan are very similar to those of locust bean gum.[13,14]

Experimental

Chromatographic separations were carried out on Whatman No. 1 paper using the following solvents: (A) 1-butanol–ethanol–water (4:1:5), upper layer; (B) ethyl acetate-pyridine–water (2:1:2), upper layer; and (C) butanone–water azeotrope. The spray reagents used were (a) aniline phthalate in 1-butanol saturated with water; (b) a solution of 5% aqueous silver nitrate, 25% ammonia, and 2 *N* sodium hydroxide[15] (1:1:2, by volume); and (c) acetonic silver nitrate and ethanolic sodium hydroxide.[16] All evaporations were carried out under reduced pressure at 35–40°. The optical rotations given are at equilibrium. Melting points are uncorrected.

Isolation of the Galactomannan.—Seeds from *Gleditsia amorphoides* were fed through a mill which was not fitted with a screen; until after several repetitions of this operation practically all the seeds were broken into several pieces. The split seeds were extracted with warm (60°) water (20 g. in 1 l.), with constant mechanical stirring during 6 hr.; this procedure was repeated until no further precipitate was obtained when the extract was added to two volumes of ethanol. The combined extracts were filtered while warm through glass wool and centrifuged, and the supernatant was poured with vigorous stirring into two volumes of ethanol where the crude polysaccharide precipitated as long fibers. The liquors were decanted and the product was squeezed in fine cloth and left overnight under alcohol. The product was dried by solvent exchange (absolute ethanol and ether) and finally in a vacuum desiccator at room temperature, yield 28–30%.

Purification.—The crude product (10.0 g.) was dissolved in 2 l. of distilled water at 50°, the solution was cooled to room temperature and centrifuged, and 400 ml. of ethanol were added to the supernatant without any precipitate appearing after 8 hr. Another 100 ml. were added and the solution was left overnight. A small brown precipitate (310 mg.) was centrifuged out and another 100 ml. of ethanol was added with no precipitation; by adding 150 ml. more, a precipitate appeared which was left overnight, centrifuged, and dried as above, yield 8.9 g. (89%). The product precipitated at a concentration of ethanol between 22 and 26% (wt. of ethanol/wt. of solution) and contained <0.4% nitrogen; $[\alpha]^{18}D$ +22.4° (*c* 0.8, water). This purification was repeated twice without any change in the optical rotation. The polysaccharide is precipitated by Fehling solution but it does not reduce it even at 100°.

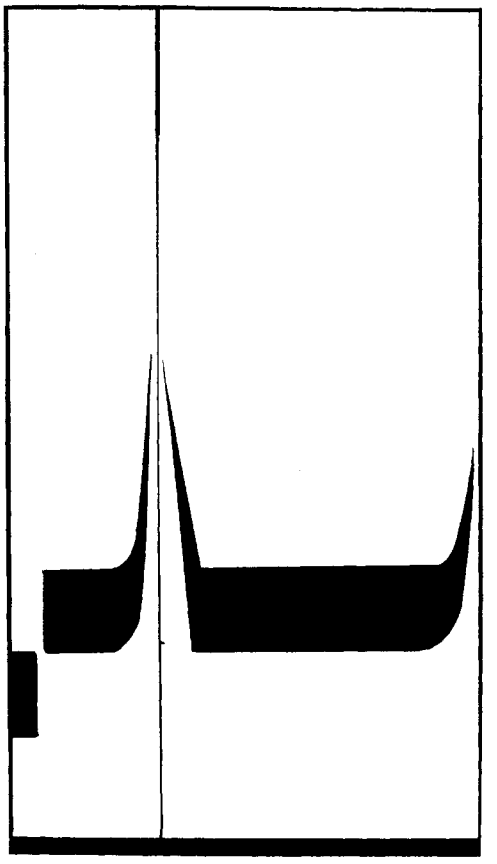

Figure 1.—Sedimentation diagram.

Acetylation.—The purified polysaccharide (1.0 g.) was dispersed in formamide (50 ml.) by shaking it at room temperature for 2 days. Anhydrous pyridine (15 ml.) was added, followed by acetic anhydride (10 ml.), the latter being added dropwise during 2 hr. After keeping overnight the brown viscous solution was poured with stirring into water; the greyish white precipitate produced was filtered, washed with water, and dried by solvent exchange (ethanol, petroleum ether) and in a vacuum desiccator at room temperature. The acetylated product was dissolved in acetone (80 ml.) and the insoluble portion (200 mg.) was centrifuged; this residue was suspended in fresh acetone (25 ml.), stirred for 1 hr., and centrifuged again. The combined acetonic extracts were poured into water and dried as above: yield 1.1 g., 40.73% acetyl, $[\alpha]^{25}D$ −18.1° (*c* 0.5, chloroform) and $[\alpha]^{25}D$ +24.9° (*c* 0.5, acetone).

Regeneration of the Galactomannan from Its Acetate.—A solution of 1.2 g. of the acetate in 35 ml. of acetone was heated under reflux in the presence of 45% potassium hydroxide (35 ml.). When the reaction was completed, the aqueous lower layer, which had become very viscous, was separated from the acetonic layer and poured with stirring into acidified ethanol, the precipitate was centrifuged out, dissolved again in water, and reprecipitated with acidified ethanol. Another reprecipitation in the same manner but using neutral ethanol gave the purified galactomannan which was dried as above: yield 450 mg., $[\alpha]^{22}D$ +23.6° (*c* 0.5, water).

Infrared Spectra.—The spectra were measured on an Infracord using a film of polysaccharide. This was obtained by concentrating to dryness a 0.5% solution of the product on a mercury surface, in a vacuum desiccator at room temperature.

Ultracentrifugation.—The sedimentation pattern (see Figure 1) was obtained in a Spinco Model E ultracentrifuge using a 1% water solution of the polysaccharide at a rotor speed of 52,640 r.p.m. and photographs were taken 212, 300, and 382 min. after

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obtaining full speed. The sedimentation coefficient ($s_{20,w}$), calculated in the usual way, was 0.73×10^{-13}.

Hydrolysis.—The purified polysaccharide (1.0 g.) was dissolved in 50 ml. of 1 *N* sulfuric acid and heated in a sealed tube at 100° for 8 hr. The resulting solution was neutralized (barium carbonate), passed through Amberlite IR-120 (H^+), and chromatographed using solvents A and B. Chromatograms sprayed with reagents a and c showed spots of galactose and mannose only. The solution was concentrated to a sirup and passed through a cellulose column using solvent A as eluent. Concentration of the appropriate fraction of the eluate gave D-mannose (which crystallized from aqueous ethanol), m.p. 132°, $[\alpha]^{20}D$ +14.0° (*c* 0.9, water); and phenylhydrazone, m.p. and m.m.p. 197–199°, $[\alpha]^{20}D$ +32.0° (*c* 0.5, pyridine). Evaporation of the eluate containing the D-galactose gave crystals upon nucleation with D-galactose and after recrystallization from aqueous ethanol the product had m.p. and m.m.p.165–166°, $[\alpha]^{22}D$ +81.0° (*c* 0.8, water); the *p*-nitroaniline derivative[17] had m.p. and m.m.p. 216–217°, $[\alpha]^{22}D$ −247° (*c* 0.7, pyridine).

The molar ratio of D-galactose and D-mannose in the hydrolyzate of the polysaccharide, determined by the phenol–sulfuric acid method,[18] was 1:2.7.

Determination of the Degree of Polymerization (D.P.) of the Galactomannan.—The galactomannan (340 mg.) was dispersed in a solution of potassium borohydride (300 mg.) in water (20 ml.). This reaction mixture was kept at room temperature for 72 hr. A similar experiment was carried out for 48 hr. with 300 mg. of the polysaccharide. In both cases the reaction mixture was acidified with 50% aqueous acetic acid and treated with sodium periodate (500 mg. for the first experiment and 550 mg. for the second). The pH was then adjusted to 7.5[19] by adding sodium bicarbonate and the volume of the solution was adjusted to 50 ml. with water. The reaction mixture was kept in the dark at room temperature and aliquots were withdrawn at intervals for determinations of formaldehyde[4,5,20]. The formaldehyde content of the solutions, which became constant after 90 hr., correspond to a D.P. of 116 for the galactomannan.

Periodate Oxidation of the Galactomannan.—The polysaccharide (105 mg.) was dissolved in 0.1 *N* sodium periodate (100 ml.) and the reaction was carried out in the dark at 5°. The formic acid produced was determined by titration with 0.01 *N* sodium hydroxide and the periodate consumption, by the method of Fleury-Lange.[19] After 96 hr. the liberation of formic acid and the periodate uptake became constant corresponding to 0.99 moles of formic acid and 4.80 moles of sodium periodate for each four hexose residues.

When the reaction was carried out in the same conditions but using 0.01 *N* sodium periodate the uptake of periodate after 160 hr. was 3.98 moles and the liberation of formic acid 0.99 moles for each four hexose residues.

Periodate Degradation of the Galactomannan.—To a solution of 200 mg. of the polysaccharide in 10 ml. of water was added a solution of 550 mg. of sodium periodate in 10 ml. of water and the volume was adjusted to 25 ml. with water. The oxidation was conducted in the dark at 5° and was followed polarimetrically; 60 hr. after the rotation became constant, the excess of periodate was destroyed with ethylene glycol and the solution was dialyzed for 72 hr. against running tap water. To the solution containing the periodate-oxidized galactomannan, potassium borohydride (100 mg.) was added. After 24 hr. at room temperature the reaction mixture was neutralized with dilute acetic acid and concentrated to dryness. After removing boric acid in the usual way the residue was dissolved in 1 *N* sulfuric acid and the solution was heated at 95° for 7 hr. The hydrolysate was neutralized (barium carbonate), centrifuged, and concentrated to dryness. Chromatography of the residue (solvents A and B, spray reagent b) showed spots corresponding to glycerol and erythritol. Traces of galactose and mannose were also detected. The ratio of glycerol to erythritol as determined by periodate oxidation–chromotropic acid method[4,5] was 1:2.7. When the polysaccharide that had been oxidized in such conditions as to consume 3.98 moles of sodium periodate for every four hexose residues was reduced with sodium borohydride and hydrolyzed as described above, chromatography showed not only glycerol, erythritol, and traces of galactose but also unattacked mannose. The proportion of mannose determined by the phenol–sulfuric acid method[18] corresponded to 1 mole for every four hexose residues.

Methylation of the Galactomannan.—The polysaccharide (10 g.) was subjected to ten methylation treatments by the Haworth method, four being conducted at room temperature followed by six treatments at 45–50°. After each methylation the reaction mixture was neutralized with sulfuric acid and the product was isolated by extraction with chloroform. The methylated galactomannan was isolated as a yellow glassy solid (10 g.)

Anal. Found: OMe, 41.5.

Two additional methylations by the Kuhn method[21] gave a product (4 g.) which had $[\alpha]^{25}D$ +26.4° (*c* 0.8, chloroform).

Anal. Found: OMe, 43.1.

The infrared spectrum of the methylated polysaccharide showed a weak hydroxyl band. Fractional extractions of the methylated galactomannan with mixtures of chloroform–petroleum ether (60–70°) furnished a main fraction which had $[\alpha]^{25}D$ −11.4° (acetone) and +28.3° (chloroform).

Anal. Found: OMe, 42.05.

Hydrolysis of the Methylated Galactomannan.—A solution of the methylated galactomannan (1.5 g.) in formic acid (20 ml. of a 90% solution) was heated for 1 hr. at 95°. The formic acid was evaporated and two additions of methanol (50 ml.) were subsequently made to assist in this process. The sirupy residue was then dissolved in 1 *N* sulfuric acid (70 ml.) and the solution was heated for 7 hr. at 95°. The solution was cooled, neutralized (barium carbonate), filtered, and evaporated. The residue was dissolved in methanol and the solution, after filtration, was concentrated to a light yellow sirup. This mixture of methylated sugars was separated into its components by cellulose column chromatography using solvent C, the eluate being collected in 10-ml. fractions by an automatic fraction collector. After paper chromatographic examination of every fifth tube it was possible to combine the appropriate fractions corresponding to the three methylated sugars referred to above.

Identification of 2,3,4,6-Tetra-O-methyl-D-galactose.—This component {0.325 g., $[\alpha]^{23}D$ +106° (*c* 0.5, water), lit.[22] $[\alpha]D$ +109.5° (water)} recovered from tubes 1–10 showed R_F values of 0.86 (solvent A) and 0.68 (solvent C) and corresponds to 2,3,4,6-tetra-O-methyl-D-galactose. Demethylation[23] showed that the parent sugar was galactose. Treatment of the methylated sugar with aniline in the usual way yielded N-phenyl-2,3,4,6-tetra-O-methyl-D-galactosylamine: m.p. 186–188°, $[\alpha]^{24}D$ +39.6° (*c* 0.6, acetone); lit. m.p. 186–188°,[24] $[\alpha]D$ +39° [acetone].[25]

Identification of 2,3,6-Tri-O-methyl-D-mannose.—Evaporation of fractions collected in tubes 16–34 gave a sirupy material (0.630 g.) which showed $[\alpha]^{22}D$ −11° (*c* 0.5, water); lit., for 2,3,6-tri-O-methyl-D-mannose, $[\alpha]D$ −10° (water).[26] Paper chromatography showed that it contained a major component corresponding to 2,3,6-tri-O-methyl-D-mannose, R_F 0.80 (solvent A) and 0.48 (solvent C), together with traces of a second component, probably 2,3,4-tri-O-methyl-D-galactose, R_F 0.65 (solvent A) and 0.37 (solvent C). Demethylation gave rise to mannose as the major and galactose as the minor component. Attempts to separate the two methylated components by further column chromatography failed. That the major component was 2,3,6-tri-O-methyl-D-mannose was shown by the fact that treatment with aniline in the usual way gave N-phenyl-2,3,6-tri-O-methyl-D-mannosylamine: m.p. 127–129°, $[\alpha]^{25}D$ −143° changing to −37° (*c* 0.5, methanol); lit. m.p. 127–128°,[27] $[\alpha]D$ −155° → −39° (methanol).[15]

Identification of 2,3-Di-O-methyl-D-mannose.—This component (0.320 g.) recovered from tubes 70–105 showed R_F 0.20 (solvent C), $[\alpha]^{23}D$ −17° (*c* 0.6, water), $[\alpha]^{23}D$ +6° (*c* 0.5, methanol), corresponding to 2,3-di-*O*-methyl-D-mannose; lit. $[\alpha]D$ −15.8° (water)[28] and +6° (methanol).[28] Upon demethylation this component gave mannose and, when treated with

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(28) G. L. Robertson, *ibid.*, 330 (1934).

p-nitrobenzoyl chloride,[29] 2,3-di-O-methyl-D-mannose 1,4,6-tri-*p*-nitrobenzoate was obtained: m.p. 192–194°, $[\alpha]^{22}D$ +66° (*c* 0.3, chloroform); lit.[29] m.p. 194°, $[\alpha]D$ +65° (chloroform).

(29) See ref. 12, p. 539.

Acknowledgment.—The author is indebted to Dr. T. Riqué for the gift of the seeds and to Drs. M. Bohner and J. S. Cerezo for the determinations with the ultracentrifuge.

A Method for the Esterification of Hindered Acids[1]

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The scope, limitations, and mechanism of a simple method for the esterification of hindered aliphatic and aromatic carboxylic acids are discussed.

Need for a quantity of methyl 9-anthroate prompted an examination of techniques for its synthesis other than the conventional esterification methods applicable for sterically hindered acids.[2] Esterification by the reaction[3] of methanol with the unsymmetrical anhydride of 9-anthroic acid and trifluoroacetic acid proved very successful. The extraordinary simplicity of this method led us to study the scope and limitations of the reaction with other hindered acids.[4]

Results and Discussion

Scope of the Reaction.—Two methods which are little different from the techniques useful for unhindered acids[3] were employed. Either the acid is dissolved in trifluoroacetic anhydride and the hydroxy compound is added (method A) or a mixture of the acid and hydroxy compound is treated with the anhydride (method B). In all but a few cases (involving severely hindered acids and hydroxy compounds) esterification is complete in less than 1 hr. The esters prepared by this procedure are summarized in Table I.

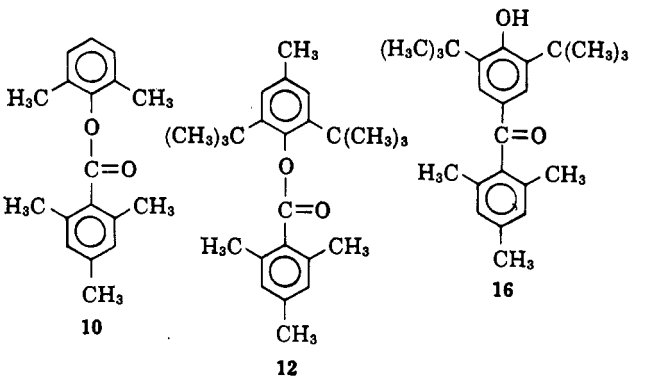
TABLE I

ESTERS PREPARED BY THE MIXED ANHYDRIDE APPROACH

Ester	Acid	Hydroxy compd.	Yield, %[a]
1	9-Anthroic	Methanol	96
2	9-Anthroic	*t*-Butyl alcohol	95
3	9-Anthroic	Phenol	96
4	10-Bromo-9-anthroic	Methanol	95
5	10-Chloro-9-anthroic	Methanol	97
6	10-Methoxy-9-anthroic	Methanol	97
7	Mesitoic	Methanol	89
8	Mesitoic	*t*-Butyl alcohol	72
9	Mesitoic	Phenol	83
10	Mesitoic	2,6-Dimethylphenol	97
11	Mesitoic	Mesitol	94
12	Mesitoic	2,6-Di-*t*-butyl-4-methylphenol	73
13	Pivalic	β-Naphthol	93
14	Triethylacetic	β-Naphthol	93
15	2-*t*-Butyl-2,2,3-trimethylbutyric	β-Naphthol	60

[a] Ester 8 is formed in 52% conversion. Ester 12 is formed in 23% conversion.

Difficulties were encountered in remarkably few cases. Mesitoic acid and 2,6-dimethylphenol readily form **10**, but mesitoic acid and 2,6-di-*t*-butylphenol provide 2,4,6-trimethyl-3′,5′-di-*t*-buty -4′-hydroxybenzophenone (**16**) in 83% yield. No ester is detected in the crude product by infrared. When both the acid and hydroxy compound are highly hindered and an alternate path, acylation of the phenol in this instance,[3c,5] is available, esterification may not occur. 2,6-Di-*t*-butyl-4-methylphenol with the 4-position blocked reacts with mesitoic acid in trifluoroacetic anhydride to yield **12**. As expected, the reaction is slow. Only 23% conversion to **12** occurs in 3 days at ambient temperature in contrast to the complete conversion of 2,6-dimethylphenol to **10** in 5 min.



The fast solvolytic reactions of *t*-alcohols with trifluoroacetic acid[3b] also influence the yields. Thus, *t*-butyl trifluoroacetate is formed competitively with ester **8**. The low conversion (Table I) presumably reflects the importance of this side reaction. The purest product and best conversion are realized with a large excess of *t*-butyl alcohol. When the alcohol is used in 1:1 ratio, olefinic by-products are formed which contaminate the product.

2,4,6-Tribromobenzoic acid (**17**) could not be esterified by this approach. When **17** is dissolved in trifluoroacetic anhydride and allowed to stand (with or without hydroxy compounds) 2,4,6-tribromobenzoic anhydride (**18**) slowly precipitates.

Mechanism.—Solutions of acids in trifluoroacetic anhydride involve several equilibria,[3b] but the major component in solution is the unsymmetrical an-

(1) Supported by Grants G14211 and G25190 from the National Science Foundation.

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