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METHYLATION OF ALCOHOLS WITH DIAZOMETHANE

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Abstract—Alcoholic hydroxyl groups were methylated by diazomethane in the presence of catalytic amounts of fluoboric acid (FBA). Primary aliphatic and unhindered secondary alcohols gave 84–98% yields of methyl ethers, while tertiary and moderately hindered secondary alcohols afforded lower yields. The order of reactivity in the methylation of the isomeric butyl alcohols, as determined in competition experiments, was $n > s > t$, and of the epimeric cholestanols, 3 $\beta(e) > 3\ \alpha(a)$. The highly hindered alcoholic hydroxyl groups of *iso*borneol was not methylated by the new reagent. The methylation of weakly acidic phenols was catalyzed by FBA. The new methylation reaction was used to prepare directly methyl ethers of desoxycorticosterone and of testosterone, and to convert ascorbic acid selectively to its 2:3:6-trimethyl ether.

THE well-known methylation of alcoholic hydroxyl groups with methyl halides, methyl arenesulfonates or dimethyl sulfate by the Williamson synthesis[1] and related procedures, requires strongly basic reaction conditions, and there seems to be no completely satisfactory general methylation procedure effective under neutral or mildly acidic conditions.

Diazomethane serves *par excellence* as the methylating agent for *acidic* hydroxyl groups. It reacts readily with carboxylic acids; the more weakly acidic phenols and enols are methylated only slowly, while alcoholic hydroxyl groups are generally not methylated at all by this reagent. A few exceptions are known, such as carbinols with electron-withdrawing groups in the α-position, which are methylated only with difficulty.[2] Aluminum alkoxides have been reported to catalyze the methylation of alcohols with diazomethane, but the authors stated that their method lacked general preparative value.[2] In our hands, β-cholestanol was not methylated by excess diazomethane in the presence of 11 mole per cent of aluminum *t*-butoxide in methylene chloride solution.

In principle, diazomethane in the presence of an acidic catalyst should methylate alcohols. However, the usual protonic acid, such as hydrochloric acid, is unsatisfactory as a catalyst, being itself consumed by reaction with diazomethane, because the intermediate methyldiazonium cation combines more rapidly with the acid anion than with the alcohol. Fluoboric acid (FBA), on the other hand, promised to serve as a useful methylation catalyst, as it would produce a relatively long-lived diazonium cation that would react with an alcohol as the nucleophile,‡[3] and it could be consumed

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† Contribution No. 2391.

‡ Cf. the reaction of diazoacetate and ethanol with various mineral acids, particularly fluoboric acid, as catalysts.

[1] A. W. Williamson, *J. Chem. Soc.* **4**, 229 (1852).
[2] H. Meerwein and G. Hinz, *Liebigs Ann.* **484**, 1 (1930).
[3] J. D. Roberts, C. M. Regan and I. Allen, *J. Am. Chem. Soc.* **74**, 3679 (1952).

in reaction with diazomethane only by some process involving rupture of a B–F bond. We have investigated the methylation of alcohols with diazomethane using FBA as a catalyst, and have found that this reaction is quite generally applicable and proceeds, within the scope described in the sequel, in high yields under mild conditions.

Methylations of hydroxyl compounds were carried out at 0–25° by adding slowly a solution of diazomethane to a solution of the alcohol containing 0·6–8·5 mole per cent of FBA. The solvents used were diethyl ether or, preferably, methylene chloride. The methyl ethers of *n*-butanol, *n*-octanol, α- and β-cholestanol were formed in appreciably higher yields in the latter solvent and, in addition, the reactions with diazomethane took place more rapidly and required less catalyst.

The results of methylations of a number of representative alcohols and phenols are recorded in Table 1. The methyl ethers of primary or unhindered secondary alcohols were formed rapidly in high (84–98%) yields by this reaction as evidenced by the methylations of *n*-butanol, *n*-octanol, *cyclo*hexanol, cholesterol, α- and β-cholestanol. Tertiary alcohols, and moderately hindered secondary alcohols, reacted more slowly, yields were lower and the reaction was accompanied by polymethylene formation, which could be minimized by operating at lower temperatures.*

Competition experiments showed that the relative rates of methylation of the three isomeric butyl alcohols were in the ratio primary : secondary : tertiary = 2·2 : 1·3 : 1·0, and those of the epimeric cholestanols were in the ratio 3β(*e*) : 3α(a) = 1·3 : 1. The rate orders were in the expected direction, but the relatively small spread indicated that the FBA-catalyzed diazomethane methylation lacked high steric selectivity. However, the 5(secondary)hydroxyl and the 6(primary)hydroxyl groups in 2:3-dimethyl ascorbic acid (Ib) were sufficiently different in reactivity to allow selective methylation of the primary in presence of the secondary hydroxyl group. Thus, ascorbic acid (Ia) was first methylated to the 2:3-dimethyl ether (Ib) by diazomethane in ether–methanol in the usual manner[4] in the absence of a catalyst; without purification, the crude enediol–diether (Ib) was converted by diazomethane in methylene chloride in the presence of 1·5 mole per cent of FBA into a hitherto unknown trimethyl ascorbic acid. The new trimethyl ether was isolated in 45% overall yield and after purification melted at 99·5–101°, $[\alpha]_D^{25}$ +33° (H_2O). It was assigned the 2:3:6-trimethyl ascorbic acid structure (Ic) on the following evidence:

(a) the maximum at 234 mμ (log ε 4·0) in the ultraviolet spectrum of the 101° compound degenerated in alkaline solution to a shoulder adjacent to the terminal absorption, and was regenerated on acidification;†

(b) after treatment of the trimethyl ether with aqueous alkali and buffering to pH 7·5, the solution consumed one mole equivalent of sodium periodate;

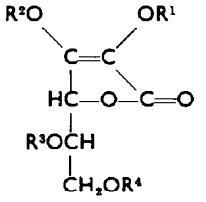
* The ethylation of secondary alcohols with FBA-catalyzed diazoethane, by an adaptation of the procedure described in the present paper, was used by W. I. Kimoto at Wisconsin to prepare *trans*- and *cis*-1-methyl-2-ethoxy*cyclo*pentane from the corresponding alcohols in 26% and 17% yields, respectively.

† These changes indicated formation of the carboxylate anion on opening of the lactone ring, and regeneration of the latter on acidification, as would be expected for a 2 : 3 : *x*-trimethyl ascorbic acid (Ic) in which the 6 (primary) hydroxyl group was blocked.[5]

[4] R. W. Herbert, E. L. Hirst, E. G. V. Percival, R. J. W. Reynolds and F. Smith, *J. Chem. Soc.* 1270 (1933).

[5] F. Micheel and W. Schulte, *Liebigs Ann.* **519**, 70 (1935); F. Micheel and G. Bischoff, *Ibid.* **525**, 66 (1936); W. N. Haworth, E. L. Hirst, F. Smith and W. J. Wilson, *J. Chem. Soc.* 829 (1937).

(c) the infrared spectral characteristics of the new compound were in accord with the structure (Ic).



Ia, $R^1 = R^2 = R^3 = H$
Ib, $R^1 = R^2 = CH_3$, $R^3 = R^4 = H$
Ic, $R^1 = R^2 = R^4 = CH_3$, $R^3 = H$

The hindered hydroxyl group of *iso*borneol could not be methylated by this method, even under forcing conditions. Triphenylcarbinol also failed to undergo methylation, perhaps because of preferential formation of triphenyl-carbonium fluoborate as evidenced by the color of the solution (halochromism).

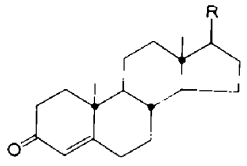
The new methylation reaction evidently occurs directly at the alcoholic oxygen atom with retention of the original configuration of the carbinol. The methyl ethers which are thus readily obtained are epimeric to those afforded, with inversion, by the alcoholysis of carbinyl tosylates and halides. For example, Nace[6] obtained α-cholestanyl methyl ether in 73% yield by methanolysis of β-cholestanyl tosylate, and the β-ether in 23% yield from the α-tosylate, together with olefins resulting from eliminations. On the other hand, the FBA-catalyzed diazomethane methylation afforded α-cholestanyl methyl ether from α-cholestanol, and the β-ether from β-cholestanol, in 98% yields, cf. Table 1. In contrast, cholesterol gave the same methyl ether[7] by each of the two paths. The nucleophilic solvolysis of cholesteryl tosylate (or chloride) proceeds by unimolecular substitution via a non-classical carbonium ion wherein the homoallylic π-electron center participates to effect overall retention of configuration.[8] The methylation of cholesterol by FBA-catalyzed diazomethane, however, proceeds undoubtedly *per se* with complete retention of configuration, without involving any part of the C_3–C_6 homoallylic system, as evidenced by the analogous steric course of methylation of the saturated cholestanols.

Newman and Beal[9] have reported that the formation of α-alkoxyketones from diazoketones and alcohols is catalyzed by boron trifluoride ethereate. We have found this reagent[10] also to be effective in catalyzing the methylation of alcohols with diazomethane. For example, the yield of β-cholestanol methyl ether was essentially unchanged by replacing the FBA catalyst with an equimolar amount of boron trifluoride etherate.

The new reagent provides a unique tool for the methylation of certain alcohols containing other sensitive groups. For example, in addition to the ascorbic acid case (see above), desoxycorticosterone (IIa) afforded directly 21-methoxyprogesterone

[6] H. R. Nace, *J. Amer. Chem. Soc.* **74**, 5937 (1952).
[7] W. Stoll, *Z. Physiol. Chem.* **207**, 147 (1932).
[8] C. W. Shoppee, *J. Chem. Soc.* 1147 (1946); S. Winstein and R. Adams, *J. Amer. Chem. Soc.* **70**, 838 (1948); E. M. Kosower and S. Winstein, *Ibid.* **78**, 4347, 4354 (1956).
[9] M. S. Newman and P. F. Beal, *J. Amer. Chem. Soc.* **72**, 5161 (1950).
[10] Since the manuscript of our preliminary communication, *J. Amer. Chem. Soc.* **80**, 2584 (1958), was written, similar observations were reported by E. Müller and W. Rundel, *Angew. Chem.* **70**, 105 (1958)

(IIb), while testosterone (IIc) gave the hitherto unknown 17β-methoxyandrost-4-ene-3-one (IId), m.p. 127–127·5°. These transformations are difficult, if not im-



IIa, R=$COCH_2OH$ IIc, R=OH
IIb, R=$COCH_2OCH_3$ IId, R=OCH_3

possible, by any previously known direct method of methylation.

The usually sluggish reaction of weakly acidic phenols with diazomethane was also shown to be catalyzed by FBA. Estradiol was thus converted directly to the dimethyl ether[11] in 81% yield under conditions which, although forcing, gave no reaction at all in the absence of the catalyst. Other weakly acidic phenols of p*K*a 9·5 to 10·2 gave poor to fair yields of methyl ethers.

EXPERIMENTAL*

Diazomethane (DM)

(*a*) *From* N-*nitroso*-N-*methylurea*. Solutions of diazomethane (DM) in diethyl ether, and in methylene chloride, were prepared by reported procedures.[12] The solutions were dried over potassium hydroxide pellets and the concentration of DM was determined by reaction of an aliquot with excess benzoic acid.

(b) *From* N-*nitroso*-N-*methyl*-N′-*nitroguanidine*. A modification of the procedure of McKay *et al.*[13] was used to prepare solutions of DM in methylene chloride. A slow stream of nitrogen was passed through the reaction flask to dilute the DM in the gaseous phase and to sweep it into the distillation and absorption assembly. Distillation of DM was discontinued when about 60–65% of the theoretical amount had been collected, while the distillate still showed a pale yellow color; thus the amount of water carried over from the reaction flask was minimized. All DM solutions were dried and analyzed as described above.

Fluoboric acid (FBA)

Concentrated FBA catalyst was used in all experiments listed in Table 1, as comparative methylation experiments with representative hydroxy compounds had shown that the yields of methyl ethers obtained in the presence of concentrated FBA catalyst were somewhat higher than with 50% aqueous FBA. Commercial FBA of ca. 50% concentration was concentrated further by partial evaporative distillation at 50–60°/5 mm. A pot residue of conc FBA thus obtained, which was ca. 16 N as determined by titration with standard alkali, was used in runs 1–4, 7 and 15–19 in

* All melting points of pure specimens are corrected for stem exposure. Ultraviolet spectra were determined with a Model 11 MS Cary Recording Spectrophotometer, and 95% ethanol was employed as solvent.

[11] Y. Urusibara and T. Nitta, *Bull. Chem. Soc. Japan* **16**, 179 (1941); C. A. **35**, 8210[1] (1941), obtained 17β-estradiol dimethyl ether, m.p. 161–162°, in 60% yield by reaction of 17β-estradiol-3-methyl ether with sodium and subsequent heating with dimethyl sulfate in benzene.

[12] F. Arndt, in *Organic Syntheses*, Coll. Vol. II, 165; R. E. Lutz, P. S. Bailey, M. T. Clark, J. F. Codington, A. J. Deinet, J. A. Freek, G. H. Harnest, N. H. Leake, T. A. Martin, R. J. Rowlett, Jr., J. M. Salsbury, N. H. Shearer, Jr., J. D. Smith and J. W. Wilson, *J. Amer. Chem. Soc.* **68**, 1813 (1946).

[13] A. F. McKay, *J. Amer. Chem. Soc.* **70**, 1974 (1948); A. F. McKay, W. L. Ott, G. W. Taylor, M. N. Buchanan and J. F. Crooker, *Canad. J. Res.* **28B**, 683 (1950).

TABLE 1. METHYLATION OF ALCOHOLIC AND PHENOLIC HYDROXYL GROUPS WITH DIAZOMETHANE IN THE PRESENCE OF FLUOBORIC ACID

Run	Hydroxy compound	mmoles	Diazo-methane, mmoles	Solvent[a]	Fluoboric acid mmoles	Methyl ethers based on hydroxy compound	% yield based on diazo-methane
	Primary alcohols						
1	*n*-Butyl alcohol	40·6	18·1	A	1·14		53[b]
2	*n*-Butyl alcohol	40·0	15·0	B	1·14		82[b]
3	*n*-Octyl alcohol	85·0	130·0	A	1·82	84[c]	55
4	*n*-Octyl alcohol	81·0	120·0	B	0·45	87[c]	59
5	L-Ascorbic acid	4·0	12·6[d]	[d]			
			5·8[e]	B	0·063	45[f]	31[g]
6	Desoxycorticosterone	0·3	1·0	B	0·0057	19	6
	Secondary alcohols						
7	*s*-Butyl alcohol	41·0	18·1	A	1·14		46[b]
8	*cyclo*Hexanol	90·0	120·0	B	0·91	92[c]	69
9	Cholesterol	1·0	3·43	B	0·0085	95[h]	28
10	α-Cholestanol	0·26	0·45	B	0·0057	65[h]	37
11	α-Cholestanol	0·26	1·26	B	0·0057	98[h]	20
12	β-Cholestanol	0·26	0·45	B	0·0057	70[h]	40
13	β-Cholestanol	0·26	0·82	B	0·0057	98[h]	31
14	Testosterone	8·0	17·6	B	0·68	22·5[i]	10
	Tertiary alcohols						
15	*t*-Butyl alcohol	40·8	18·1	A	1·14		39[b]
16	*t*-Butyl alcohol	14·3	29·0	A	0·80	45[b]	22
17	*t*-Amyl alcohol	11·4	14·3	B	0·34	66[b]	53
18	Dimethylphenyl-carbinol	45·0	90·0	A	1·82	30	15
	Competition experiments						
	n-Butyl alcohol	40·6					
19	*s*-Butyl alcohol	40·6	20·6	A	1·14	$n : s : t =$ 2·2 : 1·3 : 1·0[b]	
	t-Butyl alcohol	40·6					
20	α-Cholestanol	0·26	0·75	B	0·0057	59[h] $\beta : \alpha = 1·3 : 1$	
	β-Cholestanol	0·26				75[h]	
	Sec alcohol and phenol						
21	17β-Estradiol	1·0	5·0	B	0·026	25[j,k]	5
22	17β-Estradiol	0·5	10·7	B	0·02	81[j,k]	4
	Phenols						
23	Estrone	0·5	2·0	B	0·012	13[j]	4
24	Estrone	0·5	5·3	B	0·02	51[j]	5
25	*p*-Hydroxybiphenyl	0·5	5·3	B	0·0085	41[j]	4
26	1:3:5-Xylenol	1·0	10·2	B	0·0085	30[b]	3

[a] A = diethyl ether; B = methylene chloride. [b] Determined by vapor phase chromatography. [c] Isolated by fractional distillation. [d] Applied to ascorbic acid, in diethyl ether–methanol, without fluoboric acid. [e] Applied to 2 : 3-dimethyl ascorbic acid, without isolation, in B, in the presence of fluoboric acid. [f] Overall % conversion of ascorbic acid to 2 : 3 : 6-trimethyl ascorbic acid. [g] % yield calc. on second portion of diazomethane. [h] Isolated by adsorption chromatography. [i] 17β-Methoxyandrost-4-en-3-one. [j] Isolated by chemical separation and crystallization. [k] 17β-Estradiol dimethyl ether.

Table 1. This acid catalyst was added directly to the solutions of the alcohols methylated. In runs, 5, 6, 9–13 and 20–26, a 10·7 N FBA was used. This acid, prepared as described above, was made up to a catalyst stock solution A, containing 0·133 ml of the conc FBA in 25·0 ml of solution in 3 : 1 diethyl ether–methylene chloride.

Methylations of n-, s- *and* t-*butyl alcohols* (Runs 1, 2, 7 and 15, Table 1)

To a solution of the alcohol (40–41 mmoles) in 5·0 ml. of diethyl ether or methylene chloride was added 0·100 g (2·8 mole %) of FBA. The solution was cooled below 0° in a freezing mixture and a solution of DM in the appropriate solvent was added from a burette until ca. 0·4 mole equivalent had been added. The yellow color of DM was observed to disappear immediately on addition of the reagent to the alcohol solution. The reaction mixture was shaken with potassium hydroxide to neutralize the FBA, and some amorphous polymethylene was separated. The yields were determined by vapor phase chromatography (v.p.c.) on a column of dioctyl phthalate on Celite. The reaction mixtures from runs 1, 7 and 15 were subjected to v.p.c. directly, while that from run 2 was fractionally distilled before v.p.c. through a 55 cm Helipack column to remove two-thirds of the solvent. The identity of each graphically recorded main peak, and the relative amounts of alcohol and of methyl ether present in each of the reaction mixtures, were determined by comparison with standard solutions of the pure compounds. Peak areas were found to be proportional to concentrations to within 1% by weight.

A series of methylations, using the above procedure with equivalent amounts of 50% aqueous FBA instead of concentrated FBA catalyst, afforded lower yields of methyl ethers (*n*-butyl methyl ether, 49%; *s*-, 33%, *t*-, 31·5%).

Competition methylation of n-, s- *and* t-*butyl alcohols* (Run 19)

To a solution containing 40·6 mmoles each of *n*-, *s*-, and *t*-butyl alcohol and 0·07 ml (0·9 mole %) of concentrated FBA in diethyl ether was added 20·6 mmoles (0·17 mole equivalents) of DM in the same solvent. The relative amounts of the alcohols and of the methyl ethers in the reaction mixture were determined by v.p.c. The relative rates of methylation computed from these data were $n : s : t =$ 2·2 : 1·3 : 1·0.

Preparative methylations of alkyl-, cyclo*alkyl-, trialkyl- and dialkylarylcarbinols* (Runs 3, 4, 8 and 16–18)

The conditions used in the methylation of *n*-octyl alcohol, run 4, are representative for the general procedure which was also applied, with minor modifications, to the methylation of *cyclo*hexanol, *t*-butyl alcohol, *t*-amyl alcohol and dimethylphenylcarbinol. To a solution of 10·0 g of *n*-octyl alcohol in 20·0 ml of methylene chloride, containing ca. 0·023 g of conc FBA catalyst, which was cooled below 0°, was slowly added from a burette a solution of DM in methylene chloride. During the course of the reaction, a further portion of ca. 0·017 g of conc FBA catalyst was added. When 120·0 mmoles of DM had been added, a further portion of 0·5 g of *n*-octyl alcohol was added, which caused immediate decolorization of the excess of yellow DM present in the reaction mixture. The total amounts of reagents used represented a 1 : 1·5 molar ratio of the alcohol to DM. The FBA was removed with potassium hydroxide, and the solution was filtered to remove a small amount of polymethylene.

The solvent was removed by distillation and the residue was warmed for 45 min with metallic sodium to react with a small excess of the alcohol. The product was fractionally distilled to afford a first fraction of b.p. 53–65°/16 mm, which amounted to 0·80 g of somewhat impure *n*-octyl methyl ether as evidenced by its infrared spectrum; and a main fraction of pure methyl ether, b.p. 69–70°/18 mm, which amounted to 9·35 g (80·5%). The total yield of n-*octyl methyl ether* was 87%. An analogous methylation (run 3) of *n*-octyl alcohol in diethyl ether instead of methylene chloride, afforded a slightly reduced yield of methyl ether (84%), and required a considerably higher proportion of FBA catalyst (see Table 1).

The product obtained by methylation of *cyclo*hexanol in methylene chloride solution (run 8) by the above procedure gave on fractional distillation a first fraction of somewhat impure methyl ether, b.p. 35–52°/43 mm. The amount of cyclo*hexyl methyl ether* contained in this fraction was determined by infrared spectroscopy, and represented 9% yield. The main fraction of methyl ether, b.p. 52°/42 mm, amounted to 83% yield, the total yield being 92%.

The methylation of *t*-butyl alcohol in diethyl ether, run 16, by the same procedure, was accompanied by copious polymethylene formation. Analysis of the reaction mixture by v.p.c. indicated a 45% yield of t-*butyl methyl ether* and 46% of unreacted alcohol.

Dimethylphenylcarbinol was methylated in diethyl ether with a two-fold excess of DM (run 18). The reaction was slow and polymethylene formation was copious. Fractional distillation did not afford complete separation of the reaction mixture into pure components. The fractions obtained were analyzed by means of infrared and NMR techniques, and were found to contain a total amount of *dimethylphenylcarbinyl methyl ether* representing ca. 30% yield.

Attempted methylation of triphenyl carbinol

Triphenyl carbinol formed a deep orange-yellow solution, indicative of the presence of trityl ions, on addition of 16 N FBA catalyst in methylene chloride. To this solution was added a two-fold molar excess of DM solution in methylene chloride. The carbinol was recovered unchanged.

Methylations of sterols (Runs 9–13)

The following procedure, used in the methylation of β-cholestanol (run 13) is representative of the general conditions used, with changes in proportions of DM indicated in Table 1, also in the methylations of α-cholestanol and cholesterol. To a stirred solution of 0·100 g (0·26 mmole) of β-cholestanol, m.p. 142–142·5°, in 5·0 ml of methylene chloride, containing 0·1 ml (2·2 mole %) of FBA solution A, was added over a period of five min 2·40 ml of a 0·342 M solution of DM in methylene chloride, which had been cooled in a Dry Ice–acetone bath. This amount represented a 1 : 3·2 molar ratio of β-cholestanol to DM. The colorless reaction mixture, which contained very little polymethylene, was diluted with methylene chloride, filtered, washed with aqueous sodium bicarbonate solution and water, dried over anhydrous sodium sulfate, and evaporated to dryness in a stream of nitrogen and finally at reduced pressure (water aspirator). The methylation product was absorbed on a 60 × 10 mm column of 3·0 g of Florisil. The fractions eluted with 1 : 4 benzene–petroleum ether (b.p. 60–68°) amounted to 0·102 g (98%) of pure β-*cholestanyl*

methyl ether, m.p. 84–84·5°. The column was washed with diethyl ether to give a small fraction of 0·002 g of impure material, m.p. 77–93°. Methylation of cholesterol with a comparable excess (3·4 mole equivalents) of DM gave a 95% yield of the *methyl ether* (run 9), and the methylation of α-cholestanol with a larger excess (4·9 mole equivalents) of DM gave 98% yield of the respective *methyl ether* (run 11). Smaller excess amounts (1·7 mole equivalents) of DM afforded reduced yields of methyl ethers of α- and β-cholestanol (runs 10 and 12). Methylation of β-cholestanol by the above procedure, with 1·50 mole equivalents of DM, in the presence of concentrated FBA (2·2 mole %) and in the presence of an equivalent amount (2·2 mole %) of boron trifluoride etherate, afforded respectively, 38% and 33% yields of β-cholestanol methyl ether. Increase of the proportion of boron trifluoride etherate catalyst to 6·6 mole % lowered the yield of the methyl ether to 30%. Attempted methylation of β-cholestanol under the same conditions, but in the presence of 11·0 mole % of aluminum *t*-butoxide as the potential catalyst, did not produce any detectable amount of the methyl ether.

Competition methylations of α- and β-cholestanols (Run 20)

To a stirred solution containing 0·100 g (0·26 mmole) each of α- and β-cholestanol and 0·1 ml (1·1 mole %) of FBA solution A, was added over a period of 10 min 1·68 ml of a 0·445 M solution of DM in methylene chloride, which had been cooled in a Dry Ice–trichloroethylene cooling bath. The reaction mixture was worked up as described above. The quaternary mixture of unchanged epimeric cholestanols and of their methyl ethers was separated by chromatography on 10·0 g of Florisil. Elution with petroleum ether (b.p. 60–68°) afforded 0·061 g (59%) of α-cholestanol methyl ether, m.p. 60·5–62°, which was recrystallized from acetone–methanol to give 0·042 g of plates, m.p. 62–63°. Further elution with petroleum ether (b.p. 60–68°) to 3 : 17 benzene–petroleum ether (b.p. 60–68°) afforded 0·078 g (75%) of β-cholestanol methyl ether, m.p. 80–82°, which after recrystallization from methanol afforded 0·066 g of large plates, m.p. 84–85°. Elution with 3 : 7 benzene–petroleum ether (b.p. 60–68°) gave 0·036 g of recovered α-cholestanol, m.p. 180·5–182·5°, and elution with 1 : 1 benzene–diethyl ether afforded 0·022 g of recovered β-cholestanol, m.p. 138·5–141°, which after recrystallization from absolute ethanol gave 0·016 g of large plates, m.p. 141–142°.

2:3:6-*Trimethyl* L-*ascorbic acid* (Run 5)

A modification based on the procedure of Herbert *et al.*[4] was used to prepare 2:3-dimethyl-ascorbic acid. To a stirred suspension of 0·704 g (4·0 mmoles) of L-ascorbic acid (U.S.P., m.p. 190°) in a mixture of 3·0 ml of anhydrous methanol and 15·0 ml of anhydrous diethyl ether, cooled to −5 to −10°, was added during a period of 40 min 12·0 ml of a 0·465 M solution of DM in methylene chloride. At this stage of the reaction, evolution of nitrogen became slow, and it was reactivated by the addition of 5·0 ml of anhydrous methanol followed by 15·0 ml of DM solution over a period of 1 hr. The reaction mixture was kept for 15 hr at 25°, filtered, and the solvents were removed at reduced pressure (water aspirator). The crude enediol (0·811 g of a viscous syrup) was methylated further in the presence of FBA catalyst. To a stirred solution of the total enediol in 12·0 ml of methylene chloride, cooled to 0° and containing 0·25 ml of FBA solution A, was added 6·0 ml of the 0·465 M DM

solution over a period of 20 min. The evolution of nitrogen became slow at this stage, and a further portion of 0·1 ml of FBA solution A was added to the reaction mixture. Then the following successive portions of DM and FBA solutions were added: 2·0 ml of DM, 0·25 ml of FBA, 2·5 ml of DM, 0·25 ml of FBA, 2·0 ml of DM, and 0·25 ml of FBA solution A. The total amounts of reagents used were thus 5·8 mmoles of DM and 1·6 mole % of FBA catalyst added over a total period of 45 min. The reaction mixture was filtered, the amorphous residue of polymethylene was washed with a small amount of ethyl acetate, and the solvents from the combined filtrates were removed at reduced pressure (water aspirator). The syrupy crude product was dissolved in ethyl acetate, a small amount of diethyl ether was added, and the solution was seeded with 2:3:6-trimethyl ascorbic acid from an earlier run. The solution was kept for four days at −10°. It afforded clusters of fine prisms, 0·196 g (first crop), m.p. 95–98°. The mother liquor was concentrated to a syrup, and the crystallization procedure was repeated to afford 0·166 g (second crop) of prisms, m.p. 93–95°, and 0·030 g (third crop) of prisms, m.p. 88–91·5°. The combined crops, 0·392 g (45% overall yield from L-ascorbic acid) were recrystallized from ethyl acetate to afford long, slender prisms, 0·252 g (first crop), m.p. 99·5–100·5°, and 0·044 g (second crop), m.p. 99–100°. The first crop material was recrystallized twice from ethyl acetate to afford long prisms of 2 : 3 : 6-trimethylascorbic acid, m.p. 99·5–101°, $[\alpha]_D^{25}$ +33 (H_2O), λ_{max} 234 mμ (log ε 4·0), λ_{max}^{mull} 5·74 μ (α, β-unsat. γ-lactone), 6·01 (conj. C=C).

(Found: C, 49·5; H, 6·5, OCH_3, 42·3; Calc. for $C_9H_{14}O_6$: C, 49·54; H, 6·47; OCH_3, 42·67%).

2 : 3 : 6-Trimethylascorbic acid gave negative Fehling and ferric chloride tests.

To a solution of 3·2 mg of 2 : 3 : 6-trimethylascorbic acid in 10·0 ml of 40% aqueous ethanol was added 5 drops of 5% aqueous potassium hydroxide and the solution was heated to 90° for 1 hr. The ultraviolet spectrum of this solution showed only a shoulder at 233 mμ, adjacent to terminal absorption. This solution was acidified to pH2 with 5 drops of dilute hydrochloric acid and kept for 22 hr at 25°. λ_{max} 234 mμ (log ε 4·0).

Periodate cleavage of 2:3:6-*trimethylascorbic acid*

A solution of 10·3 mg of 2:3:6-trimethylascorbic acid (0·047 mmole) in 1·0 Ml of 1 N potassium hydroxide was heated on a steam bath for 10 min. The solution was diluted with 3·0 ml of water and heating was continued for an additional 20 min. The solution was cooled and adjusted to pH 7·5 with dilute acetic acid and sodium bicarbonate solutions. To the slightly basic solution was added 5·0 ml of a 0·08 M solution of sodium metaperiodate and the total volume was made up to 10·0 ml. After 2 hr the excess of periodate was determined by the usual sodium arsenite–iodine titration method, and 1·1 moles of periodate per mole of trimethylascorbic acid were found to have been consumed.

21-*Methoxyprogesterone* (Run 6)

To a stirred solution of 0·100 g (0·3 mmole) of desoxycorticosterone, m.p. 136–138,° in 5·0 ml of methylene chloride, containing 0·1 ml (1·9 mole %) of FBA solution A, was added over a period of 6 min 2·94 ml of a 0·342 M solution of DM in methylene chloride. The colorless reaction mixture was diluted with ether, filtered, washed with

aqueous sodium bicarbonate and water, and evaporated at reduced pressure (water aspirator). The residue was dried by the addition of benzene followed by evaporation again at reduced pressure. The infrared spectrum of the crude crystalline reaction product, m.p. 129–135°, showed no band in the OH stretching region. The product was chromatographed on 4·0 g of acid-washed alumina. Benzene eluted a crystalline middle fraction, 0·020 g (19% yield), m.p. 156–157°, which on recrystallization from methanol afforded 0·014 g (first crop) of the methyl ether, m.p. 158·5–159·5° (reported[14] m.p. 161–165°, m.p. 162–163°), λ_{max} 240 mμ (log ε 4·20); and 0·004 g (second crop), m.p. 156–158°. An earlier fraction of 0·009 g, m.p. 143–145°, eluted with 1 : 1 benzene–petroleum ether (b.p. 60–68°), and a later fraction of 0·037 g, m.p. 110–120°, eluted with diethyl ether, also contained substantial proportions of the methyl ether, as evidenced by their ultraviolet and infrared spectra. The yield in this reaction can undoubtedly be improved by modifying the conditions.

Testosterone methyl ether (Run 14)

To a stirred solution of 2·30 g (8·0 mmoles) of U.S.P. testosterone, m.p. 154–155°, in 25·0 ml of methylene chloride, containing 0·1 ml of catalyst stock solution of 0·200 g of concentrated FBA in 1·0 ml of dry diethyl ether, was added, at a rate of ca 2·0 ml per min 20·0 ml of a 0·345 M solution of DM in methylene chloride. This solution was kept cold during the addition by means of a "cold finger" filled with Dry Ice, which was immersed in the dropping funnel containing the DM solution. After the addition was complete two further 0·1 ml portions of catalyst solution were introduced at 5-min intervals, followed by a further 31-ml portion of DM solution. The total amounts of DM was thus 17·6 mmoles, and of FBA, 0·68 mmole. The reaction mixture was stirred for 20 min after addition of DM was complete. It was diluted with methylene chloride, filtered, the filtrate was washed with water, aqueous sodium bicarbonate, and water, and dried over anhydrous sodium sulfate. The solvent was removed at reduced pressure to afford 2·42 g of a pale yellow viscous syrup, λ_{max} 241 mμ (log ε 4·1). The infrared spectrum showed only a slight band in the OH stretching region. The crude methylation product was chromatographed on 120 g of Florisil on a 30 × 400 mm column. The middle fractions eluted with 1 : 99 to 1 : 32 acetone–petroleum ether (b.p. 60–68°) afforded a total of 0·477 g of prisms, m.p. 112–115°. Crystallization from ethyl acetate–petroleum ether (b.p. 60–68°) gave 0·378 g (first crop) of prisms, m.p. 126·6–126·9°. Recrystallization from the same solvent mixture yielded 0·287 g of prisms, m.p. 127–127·5°, $[\alpha]_D^{25}$ +106·3 ($CHCl_3$), λ_{max} 241 mμ (log ε 4·22), $\lambda_{max}^{CCl_4}$ 5·99 μ (C=O), 6·18 μ (C=C), 9·09 μ (ether—O—).

(Found: C, 79·2; H, 9·7; OCH_3, 10·6; Calc. for $C_{20}H_{30}O_2$: C, 79·42; H, 10·0; OCH_3, 10·26%).

Earlier fractions, amounting to 0·150 g, m.p. 105–112°, that were eluted from the column with 1 : 99 acetone–petroleum ether (b.p. 60–68°), and a later fraction, amounting to 0·080 g, m.p. 103–108°, eluted with a 1 : 36 ratio of the same solvents, were combined with the total residues from the crystallizations described above and rechromatographed. An additional 0·259 g of recrystallized tetosterone methyl ether, m.p. 127–127·5° was thus obtained (total yield 22·5%). Later fractions from

[14] C. Meystre and A. Wettstein, *Helv. Chim. Acta* **30**, 1256 (1947); H. Heusser, C. R. Engel and P. A. Plattner, *Ibid.* **32**, 2475 (1949).

the original chromatogram that were eluted with 1 : 13 acetone–petroleum ether (b.p. 60–68°) afforded 0·669 g of starting material, m.p. 146–148°, which after recrystallization from acetone gave 0·510 g, m.p. 152–153·5°.

17β-Estradiol dimethyl ether (Run 22)

To a stirred suspension of 0·136 g (0·5 mmole) of estradiol, m.p. 175–177°, in 25·0 ml of methylene chloride, containing 0·25 ml of FBA solution A, was added, over a total period of 17 min, 10·5 ml of a 0·445 M solution of DM in methylene chloride, followed by a further portion of 0·1 ml of FBA solution A and 13·5 ml of the DM solution. A considerable amount of amorphous polymethylene, which was present in the colorless reaction mixture, was removed by filtration and washed with methylene chloride. The combined filtrates were washed with aqueous sodium bicarbonate, potassium hydroxide, and water, and dried over anhydrous sodium sulfate. The solvent was removed at reduced pressure and the residue crystallized from absolute ethanol to afford 0·108 g of needles (first crop), m.p. 157·5–158·5°, and 0·023 g of needles (second crop), m.p. 150–152°. Two recrystallizations of the latter material from absolute ethanol afforded 0·012 g of needles, m.p. 157–158·5°. The total yield of 17β-estradiol dimethyl ether of good quality was 80%. A further recrystallization of the combined crops melting at 157–158·5° gave 0·101 g of needles, m.p. 160·5–162° (reported,[11] m.p. 161–162°). A control experiment, under identical conditions, but without the FBA catalyst, afforded complete recovery of the 17β-estradiol.

The above procedure is also representative of the general conditions used, with changes indicated in Table 1, in the methylation of estrone (run 24).

p-*Methoxybiphenyl* (Run 25)

To a stirred solution of 0·085 g (0·5 mmole) of *p*-hydroxybiphenyl, m.p. 163–164°, in 12·0 ml of methylene chloride, which contained 0·15 ml of FBA solution A, was added 12·0 ml of a 0·445 M solution of DM in methylene chloride over a period of 9 min. The colorless reaction mixture, containing a considerable amount of amorphous polymethylene, was filtered and the solid was washed with methylene chloride. The combined filtrates were washed with aqueous sodium bicarbonate solution and with water and dried over anhydrous sodium sulfate. The solvent was removed at reduced pressure, and the residue was digested with 5% aqueous potassium hydroxide. The insoluble portion was washed with water, dissolved in methylene chloride, and the solution was dried over anhydrous sodium sulfate. Evaporation of the solvent at reduced pressure left 0·038 g (41% yield) of colorless plates, m.p. 78–80°. The *p*-methoxybiphenyl was purified by recrystallization from ethanol to give 0·022 g (first crop) of plates, m.p. 85–87° (reported,[15] m.p. 90°), and 0·012 (second crop) of plates, m.p. 74–76°. From the aqueous potassium hydroxide solution there was recovered by acidification and extraction 0·048 g (56% recovery) of *p*-hydroxybiphenyl, m.p. 163–165°.

1-*Methoxy*-3:5-*xylene* (Run 26)

The methylation of 1:3:5-xylenol, m.p. 63–65°, was carried out under conditions based on the preceding experiment, using the amounts of reagents given in

[15] A. Werner, B. Löwenstein, A. Wack, T. Frey, M. Kunz, K. Rekner, A. Ney, H. Heil, A. Scherrer, H. Schwabacher and A. Grob, *Liebigs Ann.* **322**, 135 (1902).

Table 1. The methylation mixture, after removal of the solvent, was subjected to v.p.c. on a 40 ft column of 20% Dow Corning 550 Fluid on Johns–Manville C22 firebrick. The separation of the unchanged 1 : 3 : 5-xylenol from its methyl ether was not complete. The relative peak areas were estimated to be in the ratio 1:3:5-xylenol:1-methoxy-3 : 5-xylene = 7 : 3.

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