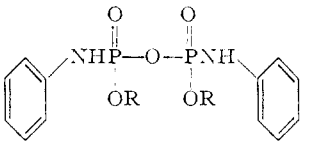
Found: C, 54.85; H, 7.90; N, 10.35) and as the dipotassium salt (*Anal.* Calcd. for $C_{12}H_{12}O_5P_2K_2$: C, 35.64; H, 2.99; N, 6.93. Found: C, 35.40; H, 3.06; N, 7.14) in yields of about 60%.

This substrate II underwent no spontaneous hydrolysis at *p*H 4.0 to *p*H 11.5 after two hours at 37°. It slowly liberated aniline at *p*H 3.5 and did so more rapidly at *p*H 2.5. Aniline was measured colorimetrically.[6] The evidence, moreover, clearly indicates that no hydrolysis of the pyrophosphate, P–O–P, bond had occurred under any of these conditions and that liberation of aniline in acid resulted solely from phosphamide, P–N, bond cleavage. If hydrolysis of the pyrophosphate bond above *p*H 4.0 had occurred phenylphosphoroamidic acid (III) would be formed. This product III[7] is essentially completely hydrolyzed after 30 minutes at *p*H 4.0, conditions at which the substrate II



I, R = $C_6H_5CH_2$
II, R = H

gives no hydrolysis. Thus III can be assayed for. Cleavage of the pyrophosphate bond in II below *p*H 4.0 is measurable simply by assay for inorganic orthophosphate. These assays showed that insignificant amounts of either phenylphosphoroamidic acid III or inorganic phosphate were produced above or below *p*H 4.0, respectively.

As regards stability to spontaneous hydrolysis this substrate II is, therefore, eminently satisfactory for enzymatic work. Extracts of intestine with high alkaline phosphatase activity[8] active against various phosphamides[9] were significantly active against this substrate II.

Preliminary results, however, suggest that the active enzyme is not alkaline phosphatase since maximum hydrolysis occurred at a new *p*H between 7.6–8.0, and of the two intestinal extracts studied the partially purified one was significantly more active against β-glycerol phosphate and β-napthyl phosphate than it was against the substrate II. The relationship of this "pyrophosphamidase" to phosphamidase and its distribution in tissues are under study that will be reported later.

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(6) F. Michael and J. Schierholt, *Ber.*, **85**, 1089 (1952).

(7) Prepared by a procedure kindly provided by Dr. J. D. Chanley.

(8) Kindly supplied by Dr. Gerhardt Schmidt.

(9) G. Schmidt and S. J. Thannhauser, *J. Biol. Chem.*, **149**, 369 (1943); G. E. Perlmann, in "A Symposium on Phosphorus Metabolism" (W. D. McElroy and B. Glass, eds.), Vol. 2, Johns Hopkins Press, Baltimore, Md., 1952, p. 167; T. Wiznick, *Arch. Biochem.*, **12**, 209 (1947).

METHYLATION OF ALCOHOLS WITH DIAZOMETHANE

Sir:

Methylation of alcohols by the Williamson synthesis requires strongly basic conditions and there is no satisfactory general methylation procedure effective under neutral or mildly acidic conditions. In principle, diazomethane with an acidic catalyst should methylate alcohols, but the usual protonic acid, such as hydrochloric acid, is unsatisfactory because it is itself methylated with diazomethane. Fluoroboric acid, however, promised to serve as a useful catalyst since it would be consumed in reaction with diazomethane only by some process involving rupture of a B–F bond.[1] This expectation was indeed realized and a novel method has been developed for methylation of alcohols in high yields under mild conditions.

Methylations of alcohols were carried out in diethyl ether or methylene chloride at 0–25° in the presence of 0.6–8 mole per cent. of fluoroboric acid. Methyl ethers of simple primary or unhindered secondary alcohols thus were formed rapidly in 84–98% yields. Moderately hindered secondary alcohols and tertiary alcohols reacted more slowly, yields were lower and methylation was accompanied by some polymethylene formation, minimized at lower temperatures. Typical cases were *n*-octanol (87%), cyclohexanol (92%), cholesterol (95%), α-cholestanol (98%), β-cholestanol (98%), dimethylphenylcarbinol (30%) and *t*-amyl alcohol (66%).

Competition experiments showed the ratios of the rates of primary, secondary and tertiary butyl alcohols = 2.2:1.3:1.0 and β (equatorial) and α (axial) cholestanol = 1.3:1. Clearly, these acid-catalyzed methylations lack high steric selectivity. Triphenylcarbinol and isoborneol could not be methylated by this method.

The new reagent provides a unique tool for the methylation of certain alcohols containing other sensitive groups. For example, testosterone and desoxycorticosterone have been converted directly to their methyl ethers—a difficult, if not impossible, transformation by any previously available direct methods. Testosterone methyl ether, which does not appear to have been described before, melts at 127–127.5°, $[\alpha]_D^{CHCl_3}$ +106.3° (found: C, 79.21; H, 9.71; OCH_3, 10.5). Ascorbic acid gave a hitherto unknown trimethyl ether, m.p. 99.5–101°, $(\alpha)^{25}D$ + 33° (H_2O); C, 49.48; H, 6.49; OCH_3, 42.3; which we consider to be 2,3,6-trimethylascorbic acid on the basis of its oxidation with weakly alkaline periodate, and by its infrared and ultraviolet spectra and the changes in the latter in the presence of dilute alkali.

Fluoroboric acid also has been shown to catalyze the otherwise sluggish reaction of weakly acidic phenols with diazomethane. Estradiol was thus converted to the dimethyl ether in 81% yield under conditions which, although forcing, gave no reaction at all in the absence of the catalyst. Other weakly acidic phenols of pK_a 9.36 to 10.17 gave poor to fair yields of methyl ethers.

Formation of α-alkoxyketones from diazoketones

(1) *Cf.* the reaction of ethyl diazoacetate and ethanol with various mineral acids, particularly fluoroboric acid, as catalysts, J. D. Roberts, C. M. Regan and I. Allen, THIS JOURNAL, **74**, 3679 (1952).

and alcohols has been reported to be catalyzed by boron trifluoride-etherate.[2] We have found this reagent also to be effective in catalyzing the methylation of alcohols with diazomethane.[3] For example, the yield of β-cholestanol methyl ether was essentially unchanged by replacing the fluoroboric acid catalyst with an equimolar amount of boron trifluoride etherate.

(2) M. S. Newman and P. F. Beal, THIS JOURNAL, **72**, 5161 (1950).

(3) Since this manuscript was written, similar observations were reported by E. Müller and W. Rundel, *Angew. Chem.*, **70**, 105 (1958).

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RECEIVED APRIL 14, 1958

CONDENSATION OF TRIMETHYLSILANOL WITH TITANIUM ISOPROPYLATE

Sir:

The preparation of glassy polymeric products containing Si–O–Ti bonds has been reported.[1] Because of interest in modified polymers, it seems worthwhile to report a simple synthesis of several monomeric compounds containing silicon and titanium.

The synthesis involves mixing trimethylsilanol and titanium isopropylate in the molar ratios desired in the product, usually in a solvent, and distilling to recover substantial yields of the product.

A typical preparation for $Ti[OSi(CH_3)_3]_4$ is given. To 0.1 mole (28.4 g.) freshly distilled titanium isopropylate in a 125-ml. distilling flask was added 70 ml. of 5.77 molar trimethylsilanol (0.4 mole) in dibutyl ether. The mixture became warm, was allowed to stand for about an hour, then distilled in vacuum to remove ether solvent and recover the reaction product. With no special precautions the recovery was 50–70% of theoretical.

The products obtained in separate preparations using appropriate ratios of silanol to titanium isopropylate are summarized in Table I.

TABLE I

Formula		$Ti(OC_3H_7)_3(OSi(CH_3)_3)$	$Ti(OC_3H_7)_2(OSi(CH_3)_3)_2$	$Ti(OSi(CH_3)_3)_4$
Carbon, %	Calcd.	45.85	41.83	35.65
	Found	45.71	41.65	35.81
Hydrogen, %	Calcd.	9.62	9.36	8.98
	Found	9.48	9.33	9.05
$n^{22}D$		1.4490	1.4408	1.4300
B.p.	°C.	114	120	100
	Mm.	13	14	2

The condensation product containing two silanols and two isopropyl groups would be expected to exhibit two arrangements if the titanium is square and planar. No separation was attempted.

Each of the titanium products was a water white liquid as prepared, but those containing isopropoxy groups developed an intense blue on standing for several months in sealed capsules.

Volatile products incompletely characterized were obtained by the distillation of trimethylsilanol and aluminum isopropylate.

The use of diethylsilanediol in place of trimethylsilanol with the appropriate isopropylate gave non-volatile polymeric substances which have not been characterized.

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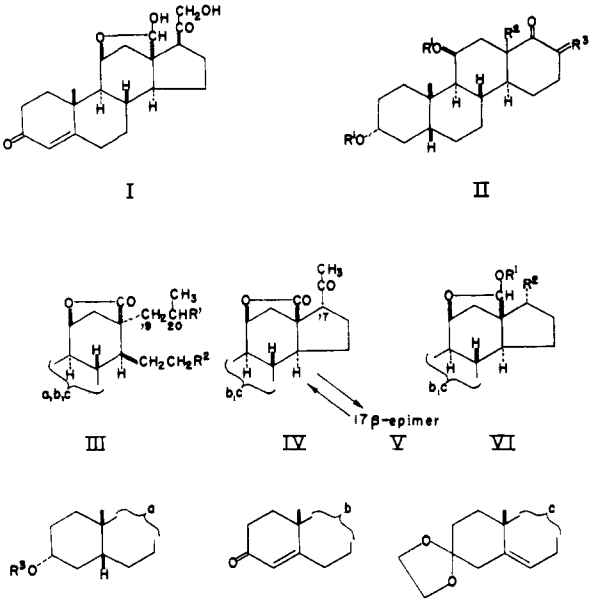
RECEIVED FEBRUARY 15, 1958

TOTAL SYNTHESIS OF ALDOSTERONE

Sir:

We disclose herewith a preparation of the adrenal hormone aldosterone (I) by a highly stereoselective total synthesis which is basically different from previous approaches.[1]

The dihydroxy-ketone II(R^1 = H, R^2 = βH, R^3 = H_2)[2] was converted into the 17-furfurylidene derivative (R^3 = CHC_4H_3O) m.p. 193–194° which, on treatment with methacrylonitrile in methanolic methoxide, was transformed into the adduct II (R^1 = H, R^2 = $-CH_2CH(CH_3)CN$, R^3 = CHC_4H_3O).[3,4] Acetylation, followed by ozonolysis, then



(1) (a) J. Schmidlin, G. Anner, J. R. Billeter and A. Wettstein, *Experientia*, **11**, 365 (1955), *et seq.* to J. S. Schmidlin, G. Anner, J. R. Billeter, K. Heusler, H. Ueberwasser, P. Wieland and A. Wettstein, *Helv. Chim. Acta*, **40**, 2291 (1957); (b) A. Lardon, O. Schindler and T. Reichstein, *ibid.*, **40**, 666 (1957).

(2) W. S. Johnson, R. Pappo and W. F. Johns, THIS JOURNAL, **78**, 6339 (1956).

(3) This product was a mixture of C_{20} epimers that could be employed in the succeeding steps without separation because the asymmetry of C_{20} was ultimately eliminated. In the preliminary study the mixture was separated at the diketone stage IIIa (R' = R^2 = $COCH_3$, R^3 = Ac) and each epimer examined separately in the succeeding reactions.

(4) *Cf.* W. S. Johnson, D. G. Martin, R. Pappo, S. D. Darling and R. A. Clement, *Proceedings*, 58 (1957).

(1) K. A. Andrianov, T. N. Janina and E. N. Khrustaleva, *Izvest. Akad. Nauk, S.S.S.R., otdel, Khim. Nauk*, 798–804 (1956); *Chem. Abstr.*, **51**, 3487 (1957).