Structure III can exist in one of four forms while IV can exist in three forms. The products that were isolated seem to be made up of one compound only in each case. It is interesting to note that the adduct III, as prepared, is yellow. Distillation at low pressure or passage through a gas chromatographic column did not decolorize the material. However, mild oxidation by air removed the yellow contaminant. The purified sample of III seems to have the same infrared spectrum as the yellow material (which analyzes exactly for $C_{10}H_{12}$). It is reasonable to suggest that the yellow color is due to a material possibly isomeric with III that is present in trace quantity.

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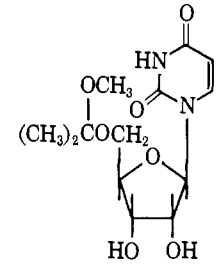
Direct Conversion of a Nucleoside to an Acid-Labile 5′-O-Alkoxyalkyl Derivative

Sir:

Direct, selective blocking of the 5′-(primary) hydroxyl of ribo- and deoxyribonucleosides is a frequently used synthetic procedure; it is presently achieved only by the classical formation of a triphenylmethyl ether.[1,2] This communication reports that a ribonucleoside can also be converted predominantly to a 5′-monosubstituted derivative by reaction with an aliphatic ketal. Furthermore, the 5′ substituent reported here is itself of potential value in syntheses of nucleosides and carbohydrates because of its lability under mildly acidic or even neutral conditions.[3]

2,2-Dimethoxypropane (10 ml.) was dissolved in a solution of uridine (0.25 g.) and di-*p*-nitrophenyl phosphate (0.01 g.) in N,N-dimethylacetamide (1.25 ml.). Portions neutralized with ammonia were chromatogramed on paper in 2-propanol–water–ammonia (7:2:1) (solvent A) and 2-propanol–1% boric acid–ammonia (7:2:1) (solvent B; papers first steeped in 1% ammonium borate, blotted, and dried). Disappearance of uridine (R_f 0.38 and 0.10) was accompanied by the formation of a less hydrophilic, borate-complexing (*cis*-α-glycol-containing) component (R_f 0.56 and 0.33)[4] which after 3 hr. comprised 75% of the ultraviolet light absorbing material; 5% unchanged uridine and a third component (R_f 0.76 in system B) were also present. The same mixture resulted when di-*p*-nitrophenyl phosphate was omitted and the reaction mixture was heated under reflux for 2 days. The major product reacted as a *cis*-α-glycol toward the periodate spray test.[5] Tri-*n*-butylamine (25 μl.) was added to the reaction conducted at 25° and volatiles were removed *in vacuo* (finally 0.5 mm., 40°). To a solution of the gum in chloroform (1 ml.) was added benzene (5 ml.), then cyclohexane (25 ml.), and the suspension was shaken for 1 hr. The precipitated gum was repurified from chloroform as above,[6] and its solution in solvent A (0.3 ml.) was applied to a column (2.7 × 32 cm.) of cellulose powder[7] in solvent A. Elution with this solvent (4.5-ml. fractions collected) effected extensive separation of the major product (fractions 25–30) from uridine (29–33). Removal of solvent *in vacuo* from fractions 25–28, and addition of benzene (9 ml.) to a solution of the residue in chloroform (2 ml.), gave white needles, 163 mg. (46%), chromatographically homogeneous in systems A and B. Addition of benzene (19 ml.) to its solution in dioxane (2 ml.) gave needles (122 mg.), m.p. 96–103° dec. *Anal.*[8] Calcd. for $C_{13}H_{20}N_2O_7 \cdot 0.5C_6H_6$: C, 54.08; H, 6.52; N, 7.89. Found: C, 54.19; H, 6.80; N, 8.03. At pH 7.25 ϵ_{max} was 10,100 (261 mμ) and 9600 (204 mμ), ϵ_{min} 2250 (231 mμ); at pH 12, ϵ_{max} was 7700 (261 mμ), ϵ_{min} 5600 (242 mμ). These absorption characteristics are indistinguishable from those of uridine,[9] indicating the absence of substitution on the uracil moiety. Elemental analysis shows that the product is not a symmetrical ketal containing two uridine residues, and it is therefore concluded to be 5′-O-1′′-methoxyisopropyluridine (I).



I

Hydrolysis of I gave a single ultraviolet-absorbing product with the R_f of uridine in solvents A, B, and 2-propanol–water (7:3; run on diethylaminoethylcellulose). The half-life of I (0.01 *M*) was 1 min. at 25° in 0.1 *M* acetate buffer, pH 4.7, and 5 min. at 100° in 0.05 *M* phosphate buffer, pH 7.2 (25°).

Other 1-alkoxyalkyl groups, namely, alkoxymethyl[10] (from chloromethyl alkyl ethers) and tetrahydropyranyl[11] and ethoxyethyl[12] (from α,β-unsaturated ethers), have been used to protect carbohydrate[10] and nucleoside[12,13] hydroxyls, although the feasibility of selectively blocking primary hydroxyls is not known. The selectivity[14] of 2,2-dimethoxypropane in the present

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(3) Acid-labile (substituted trityl) blocking groups for nucleoside 5′-hydroxyls are, for example, required for some syntheses of polynucleotides [Y. Lapidot and H. G. Khorana, *J. Am. Chem. Soc.*, **85**, 3852 (1963); G. Weimann, H. Schaller, and H. G. Khorana, *ibid.*, **85**, 3835 (1963)].
(4) 2′,3′-O-Isopropylideneuridine, which cannot form a borate complex, had R_f values of 0.59 and 0.66 in systems A and B, respectively.
(5) J. A. Cifonelli and F. Smith, *Anal. Chem.*, **26**, 1132 (1954).
(6) The benzene–cyclohexane contained the by-product(s) (R_f 0.76, system B), tributylammonium di-*p*-nitrophenyl phosphate and traces of the major product.
(7) Whatman CC31; first freed of fine particles in water.
(8) By A. Bernhardt, Mülheim, Germany.
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(13) M. Smith, D. H. Rammler, I. H. Goldberg, and H. G. Khorana, *J. Am. Chem. Soc.*, **84**, 430 (1962).
(14) Limited reaction did occur at the 2′ and 3′ positions: treatment of the by-product of the reaction with 0.01 *N* HCl for 5 min., 25°, gave equal amounts of uridine and 2′,3′-O-isopropylideneuridine. Reaction of equimolar proportions of 2,2-diethoxypropane and uridine in N,N-dimethylformamide catalyzed by relatively high concentrations of hydrogen ion gives a high yield of 2′,3′-O-isopropylideneuridine [S. Chladek and J. Smrt, *Collection Czech. Chem. Commun.*, **28**, 1301 (1963)].

instance is presumably related to the greater readiness with which simple ketals undergo alkoxyl interchanges with primary alcohols than with monohydric secondary alcohols.[15] The present reaction conditions should be applicable to other nucleosides and to ketals of ketones other than acetone.

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Microbiological Synthesis of Aldosterone from Corticosterone

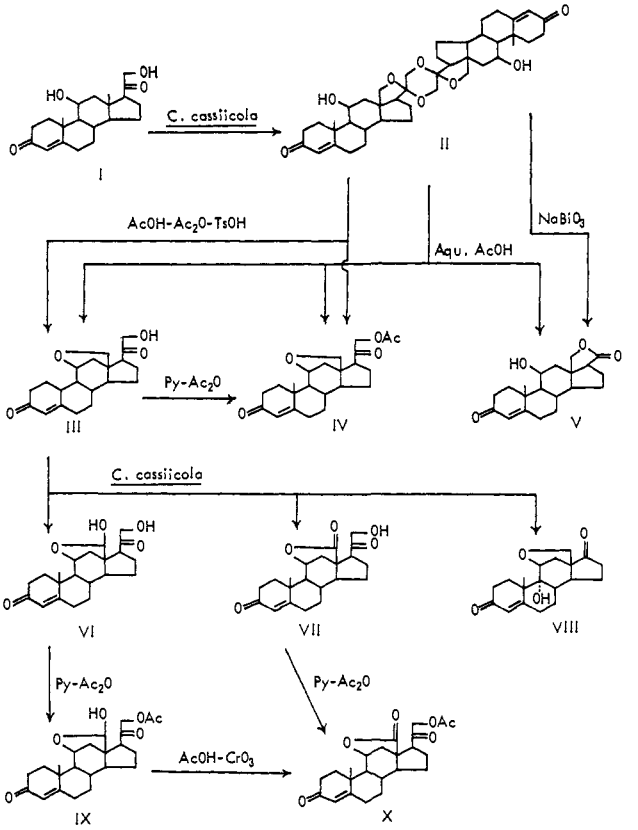
Sir:

Several investigations dealing with the partial synthesis of aldosterone have been reported in recent years.[1,2] Among these, Barton and Beaton's route to aldosterone acetate from corticosterone acetate by the felicitous utilization of a photochemical reaction is most conspicuous in view of its short path and good total yield.[2] However, the practical use of microorganisms in the course of synthesis has not been reported so far. We report here a new partial synthesis of aldosterone from corticosterone (I) through only three steps containing two transformations by microorganisms capable of introducing a hydroxyl group into the C-18 position of the steroid nuclei.[3]

Transformation of I with the resting mycelium of *Corynespora cassiicola* (IMI 56007) afforded mainly 18-hydroxycorticosterone in about 20% yield,[4,5] which was isolated as a dimer (II) due probably to its facile dimerization,[6] along with several by-products.[7]

Compound II [$C_{42}H_{56}O_8 \cdot 0.5H_2O$, mol. wt. (found) 679, m.p. 293–296°, $[\alpha]^{25}D$ +206.5° (chloroform–methanol, 1:1), ν_{max}^{Nujol} 3458, 1668, and 1616 cm.$^{-1}$][8] shows the absence of the 20-carbonyl band and 18-methyl signal in its infrared and n.m.r. spectra, respectively.

Three products (III, IV, and V; yields, 60, 10, and 5%, respectively) were obtained when an aqueous acetic acid solution of II was refluxed. The main component [III, m.p. 140–141°, $[\alpha]^{25}D$ +218°, λ_{max} 240.5 mμ (ε 15,800), $\nu_{max}^{CHCl_3}$ 3500, 1712, 1665, and 1621 cm.$^{-1}$] was converted into its monoacetate [IV, m.p. 160–161°, $[\alpha]^{25}D$ +216.4°, λ_{max} 240 mμ (ε 16,400), $\nu_{max}^{CHCl_3}$ 1751, 1728, 1667, and 1619 cm.$^{-1}$] by the usual acetylation. Acetylation of II with acetic acid–acetic anhydride in the presence of *p*-toluenesulfonic acid dominantly afforded IV with a small amount of III. In the n.m.r. spectra of III and IV, doublet of triplets signals characteristic of a proton signal on 11β-oxygen-bearing carbon in 11β,13β-bridged steroids,[9] instead of a quartet corresponding to a proton on 11β-hydroxyl-bearing



carbon, appear at τ 5.42 and 5.57 (J = 6.2 and 0.5 c.p.s.), respectively. Also the 21-methylene signals are found at τ 5.78 in III and 5.36 in IV as coalescing singlets, whereas the 18-methylene signals appear as AB-type quartets at τ 5.45 and 6.67 in III, and at 6.32 and 6.57 in IV (J = 8.2 c.p.s.). The infrared spectra of III and IV were identical in all respects with those of racemic 18-deoxyaldosterone and its 21-acetate, respectively, synthesized by Schmidlin and Wettstein.[10] The five-membered lactonic compound [V, m.p. 263–266°, $[\alpha]^{24}D$ +154.3°, λ_{max} 241.5 mμ (ε 16,500), ν_{max}^{KBr} 3406, 1770, 1645, and 1620 cm.$^{-1}$] was also obtained by so-

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(4) The use of *Cercospora melonis* [*Corynespora melonis* (Cke) Lindau][3] gave the same product, but in somewhat lesser yields.

(5) Microbiological preparation of this compound from 18-hydroxydeoxycorticosterone was recently reported [P. B. Raman and F. G. Péron, *Steroids*, **5**, 249 (1965)].

(6) We thank Dr. R. Pappo of G. D. Searle & Co. and Dr. J. Schmidlin of CIBA Aktiengesellschaft (Basel) for their kind information about the dimeric form of 18-hydroxydeoxycorticosterone derivatives.

(7) The structures of five compounds among the isolated crystalline by-products have been shown to be 6β-, 8β-, 14α-, 15β-, and 17α-monohydroxy derivatives of I (yields; 3, 5, 2, 10, and 3%, respectively). The detail of the structure elucidation of these compounds will be reported in our full paper.

(8) Elemental analyses of the compounds described here gave satisfactory values. Unless otherwise noted, optical rotations were determined in chloroform containing 1% ethanol, and ultraviolet absorption spectra were observed on solutions in 95% ethanol. N.m.r. spectra were taken with a Varian A-60 spectrometer on deuteriochloroform solutions containing tetramethylsilane as an internal reference.

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