

instance is presumably related to the greater readiness with which simple ketals undergo alkoxy 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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(15) W. L. Howard and N. B. Lorette, *J. Org. Chem.*, **25**, 525 (1960).

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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 cassicola* (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°, $[\alpha]^{25D} +206.5^\circ$ (chloroform-methanol, 1:1), ν_{max}^{Nujol} 3458, 1668, and 1616 cm^{-1}]⁸

(1) (a) K. Heusler, J. Kalvoda, Ch. Meystre, P. Wieland, G. Anner, A. Wettstein, G. Cainelli, D. Arigoni, and O. Jeger, *Experientia*, **16**, 21 (1960); (b) L. Velluz, G. Muller, R. Bardonesch, and A. Poittevin, *Compt. rend.*, **250**, 725 (1960); (c) M. E. Wolff, J. F. Kerwin, F. F. Owings, B. B. Lewis, B. Blank, A. Magnani, and V. Georgian, *J. Am. Chem. Soc.*, **82**, 4117 (1960); (d) W. Nagata, M. Narisada, and T. Sugasawa, *Tetrahedron Letters*, No. 23, 1041 (1962).

(2) D. H. R. Barton and J. M. Beaton, *J. Am. Chem. Soc.*, **82**, 2641 (1960).

(3) E. Kondo and K. Tori, *ibid.*, **86**, 736 (1964).

(4) The use of *Cercospora melonis* [*Corynespora melonis* (Cke) Lindau]⁹ 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)].

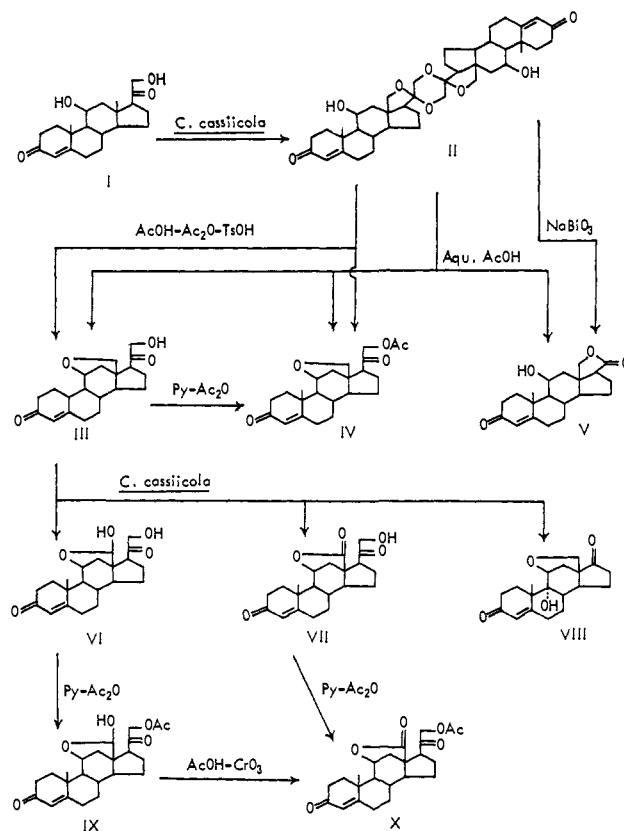
(6) We thank Dr. R. Pappo of G. D. Searle & Co. and Dr. J. Schmidlin of CIBA Aktiengesellschaft (Basel) for their kind information about the dimeric form of 18-hydroxydeoxycorticosterone derivatives.

(7) The structures of five compounds among the isolated crystalline by-products have been shown to be 6 β -, 8 β -, 14 α -, 15 β -, and 17 α -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.

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°, $[\alpha]^{25D} +218^\circ$, λ_{max} 240.5 $m\mu$ (ϵ 15,800), $\nu_{max}^{CHCl_3}$ 3500, 1712, 1665, and 1621 cm^{-1}] was converted into its monoacetate [IV, m.p. 160–161°, $[\alpha]^{25D} +216.4^\circ$, λ_{max} 240 $m\mu$ (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 11 β -oxygen-bearing carbon in 11 β ,13 β -bridged steroids,⁹ instead of a quartet corresponding to a proton on 11 β -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°, $[\alpha]^{24D} +154.3^\circ$, λ_{max} 241.5 $m\mu$ (ϵ 16,500), ν_{max}^{KBr} 3406, 1770, 1645, and 1620 cm^{-1}] was also obtained by so-

spectra were taken with a Varian A-60 spectrometer on deuteriochloroform solutions containing tetramethylsilane as an internal reference.

(9) K. Tori, T. Tomita, H. Itazaki, M. Narisada, and W. Nagata, *Chem. Pharm. Bull.* (Tokyo), **11**, 956 (1963).

(10) J. Schmidlin and A. Wettstein, *Helv. Chim. Acta*, **44**, 1596 (1961).

dium bismuthate oxidation¹¹ of II. In the n.m.r. spectrum of V, a quartet signal at τ 5.48 corresponding to the proton on 11 β -hydroxyl-bearing carbon and an AB-type quartet at τ 4.90 and 5.95 ($J = 10.0$ c.p.s.) arising from the 18-methylene group are found. The infrared spectra of this compound in the various states (KBr, CHCl₃, and CH₂Cl₂) were in agreement with those of an authentic specimen of 11 β ,18-dihydroxyandrost-4-ene-17 β -carboxylic acid 18,20-lactone.^{12,13}

Incubation of III with *C. cassiicola* (IMI 56007) produced three crystalline compounds (VI, VII, and VIII; yields, 17, 3, and 2%, respectively). The main product [VI, m.p. 165–167°, [α]^{24D} +163.3°, λ_{\max} 240.5 m μ (ϵ 16,600), $\nu_{\max}^{\text{CHCl}_3}$ 3721, 3571, 3461, 1705, 1667, and 1618 cm.⁻¹] was identified as aldosterone¹⁴ by mixture melting point determination and by comparison of infrared and n.m.r. spectra with those of an authentic specimen. Partial acetylation of VI gave a 21-monoacetate [IX, m.p. 193–195°, [α]^{23.5D} +127.5°, $\nu_{\max}^{\text{CHCl}_3}$ 3711, 3591, 3431, 1738, 1718, 1666, and 1617 cm.⁻¹], which was converted into a five-membered lactone [X, m.p. 202–204°, [α]^{23.5D} +118.4°, $\nu_{\max}^{\text{CHCl}_3}$ 1772, 1750, 1728, 1669, and 1621 cm.⁻¹] by chromic acid oxidation. Physical constants as well as infrared and n.m.r. spectra of X agreed with those of an authentic specimen of 18-dehydroaldosterone 21-acetate prepared in our laboratory.^{14,9} The second product [VII, m.p. 208–213°, $\nu_{\max}^{\text{CH}_2\text{Cl}_2}$ 3486, 1772, 1710, 1671, and 1621 cm.⁻¹] was identified as 18-dehydroaldosterone by both comparison of infrared spectra¹⁵ and the preparation of X by usual acetylation. The remaining compound [VIII, m.p. 234–236°, λ_{\max} 241 m μ (ϵ 15,800), $\nu_{\max}^{\text{Nujol}}$ 3421, 1728, 1659, and 1624 cm.⁻¹] lacks the 20-carbonyl band and 21-methylene signal in its infrared and n.m.r. spectra, respectively, and instead has a carbonyl in a five-membered ring and only one tertiary hydroxyl group which shifts the 19-methyl n.m.r. signal downfield by about 0.2 p.p.m. from its position in III.^{3,16} Furthermore, the 18-methylene signal appears at τ 5.97 and 6.58 as an AB-type quartet and the 11 α -proton signal is found at τ 5.52 as a second-order tripletlike pattern. In addition, from other physical and chemical evidence¹⁷ VIII was elucidated to be 9 α -hydroxy-11 β ,18-epoxyandrost-4-ene-3,17-dione. The total yield of this synthesis of VI from I is about 2% at present, but a possible improvement for increasing the yield might be expected in the future.

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(11) C. J. W. Brooks and J. K. Norymberski, *Biochem. J.*, **55**, 371 (1953).

(12) R. Neher and A. Wettstein, *Helv. Chim. Acta*, **43**, 623 (1960). We thank Drs. A. Wettstein and R. Neher of CIBA Aktiengesellschaft (Basel) for sending us copies of the infrared spectra of this compound.

(13) In a nitrogen atmosphere, treatment of II with aqueous acetic acid (refluxing) gave only a trace of the lactone V. From this result as well as that in the report by F. G. Péron, *Endocrinology*, **70**, 386 (1962), it might be considered that 18-hydroxycorticosterone derivatives are unstable in air.

(14) The infrared spectrum of VI was also identical with that reported by S. A. Simpson, J. F. Tait, A. Wettstein, R. Neher, J. V. Euw, O. Schindler, and T. Reichstein, *Helv. Chim. Acta*, **37**, 1163 (1954); the physical constants agreed well with those reported by R. E. Harman, E. A. Ham, J. J. DeYoung, N. G. Brink, and L. H. Sarett, *J. Am. Chem. Soc.*, **76**, 5035 (1954).

(15) E. Vischer, J. Schmidlin, and A. Wettstein, *Experientia*, **12**, 50 (1956).

(16) Also refer to K. Tori and E. Kondo, *Steroids*, **4**, 713 (1964).

(17) The detail of the structure determination of VIII will appear in our full paper.

K. Takeda, Director of this laboratory, for their helpful advice and encouragement, and also to Drs. W. Nagata and S. Hayakawa for their valuable discussions on this work.

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Acid-Catalyzed Reactions of Phenols with Dimethyl Sulfoxide and Dicyclohexylcarbodiimide

Sir:

One of the mildest methods available for the oxidation of alcohols to aldehydes and ketones consists of their acid-catalyzed reaction with dimethyl sulfoxide (DMSO) and dicyclohexylcarbodiimide (DCC).¹ We now wish to report similar reactions applied to phenols.²

The predominant reaction with most simple phenols is the introduction of thiomethoxymethyl groups in the available *ortho* positions. Thus, phenol itself reacts exothermally with 3 equiv. of DCC and 0.5 equiv. of anhydrous orthophosphoric acid in mixtures of DMSO and benzene to give 2-(thiomethoxymethyl)phenol (Ia, 27%, $\lambda_{\max}^{\text{MeOH}}$ 278 m μ (ϵ 2900); $\lambda_{\max}^{\text{OH}^-}$ 242 and 297 m μ (ϵ 8300 and 4100)) and 2,6-di(thiomethoxymethyl)phenol (Ib, 17%, $\lambda_{\max}^{\text{MeOH}}$ 283 m μ (ϵ 2870); $\lambda_{\max}^{\text{OH}^-}$ 307 m μ (ϵ 5530)). Desulfurization of Ia and Ib with Raney nickel in methanol rapidly and quantitatively gave *o*-cresol and 2,6-dimethylphenol, respectively. Similar *ortho*-alkylation products were obtained from other phenols. Thus³: *o*-cresol gave 28% Ic; 2,5-dimethylphenol gave 35% Id; *o*-nitrophenol gave 38% Ie (m.p. 78–79°); *p*-nitrophenol gave 26% If (m.p. 127.5–128.5°), 11% Ig (m.p. 76.5–77.5°), and 15% Ih (m.p. 148–149°); α -naphthol gave 2-(thiomethoxymethyl)-1-naphthol. Desulfurization of each of the unnitrate products gave an excellent yield of the appropriate methylphenol. The n.m.r. spectra of products of type I are characterized by three-proton singlets (SCH₃) at 112–124 c.p.s. and by two-proton singlets (ArCH₂S) at 221–231 c.p.s. A similar reaction with estrone gave both 2-(thiomethoxymethyl)estrone (m.p. 205–207°, two aromatic protons as singlets at 399 and 422 c.p.s.) and 4-(thiomethoxymethyl)estrone (m.p. 154–156°, two doublets with $J = 8$ –9 c.p.s. centered at 403 and 429 c.p.s.).

Several other types of products were also formed, depending upon the nature of the phenol. Thus, with more acidic phenols, O-alkylation was observed. In the case of *p*-nitrophenol 3% of IIa (m.p. 50–51°) and 14% of IIb (m.p. 61–62°) were obtained, while *o*-nitrophenol gave low yields of both IIc and IId as distillable oils. These products were nonphenolic (infrared and ultraviolet) and showed three-proton singlets (SCH₃) at 135–138 c.p.s. and two-proton singlets (OCH₂S) at 314–319 c.p.s. in their n.m.r. spectra. Acid hydrolysis readily gave the appropriate phenol, formaldehyde, and methyl mercaptan, and both IIa

(1) K. E. Pfitzner and J. G. Moffatt, *J. Am. Chem. Soc.*, **85**, 3027 (1963), and in press.

(2) Independently K. E. Pfitzner, J. P. Marino, and R. A. Olofson, *J. Am. Chem. Soc.*, **87**, 4658 (1965), have studied similar reactions.

(3) All compounds described gave correct elemental analyses.