The strong interaction between dissolved oxygen and water revealed by our results and the even stronger interaction between dissolved oxygen and saturated hydrocarbons such as hexane revealed by the results of others[1,2] suggest bonding between the molecular oxygen and the hydrogen of the solvent. This seems reasonable in view of the fact that the oxygen molecule is a diradical and the hydrogen atom is well known to form bonds simultaneously with two other atoms such as with the oxygen atoms in the dimer of acetic acid, with the boron atoms in $B_2H_6$ and with the oxygen atoms on adjacent water molecules.

In the case of oxygen dissolved in water possible structures formed when the oxygen molecule attached itself to two hydrogen atoms would be a bridge between two water molecules and alternatively a five-membered ring involving one molecule of water. In the case of oxygen dissolved in saturated hydrocarbons such as hexane, a plausible structure would be the six-membered ring in which the oxygen molecule was attached to the hydrogens on adjacent carbon atoms as well as a bridge between the hydrogen atoms on adjacent solvent molecules.

The new hydrogen bonds suggested here differ from those bridge hydrogen bonds previously recognized in that three rather than two or four electrons participate with the proton in their midst in forming the bridge between the other two atoms.

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## STEREOCHEMICAL CONTROL OF ANGULAR METHYLATION. A STEREOSELECTIVE TOTAL SYNTHESIS OF A 9,11-DEHYDROSTEROID

*Sir:*

Certain previous total syntheses of steroids, namely, estrone,[1] epiandrosterone,[2] 3β,11β-dihydroxyandrostane-17-one,[3] and testosterone,[4] have embodied a common sequence for the elaboration of ring D involving, as key intermediates, the corresponding 18-nor-D-homo compounds (*cf.* formula III) which, after protective condensation with an aldehyde, were methylated, then oxidized to the dibasic acids and recycled to yield the five-membered ring D compounds (*cf.* formulas III → IV → V → VI). While the yields for this angular methylation-ring contraction sequence were generally good, the stereochemical course of the methylation step was always unfavorable giving a preponderance of the unnatural isomer in which the rings were *cis*-locked. This behavior is typified by the results with 2-benzylidene-1-decalone which, on methylation, afforded the *cis* and *trans* 9-methyl homologs in 68 and 23% yields, respectively.[5]

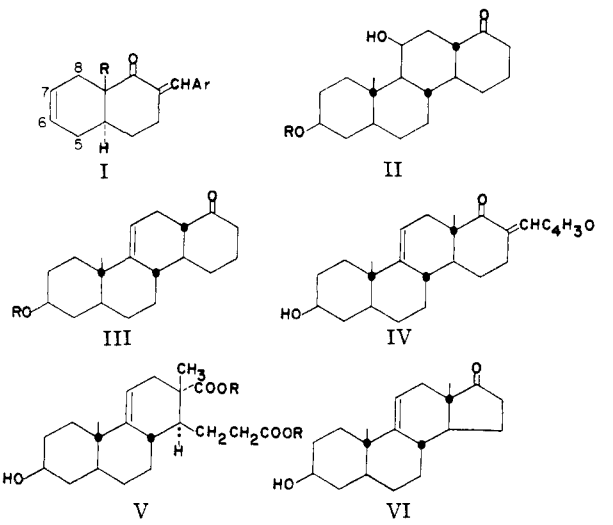
(1) W. S. Johnson, D. K. Banerjee, W. P. Schneider, C. D. Gutsche, W. E. Shelberg and L. J. Chinn, THIS JOURNAL, **74**, 2832 (1952).

(2) W. S. Johnson, B. Bannister and R. Pappo, *ibid.*, **78**, 6331 (1956).

(3) W. S. Johnson, R. Pappo and W. F. Johns, *ibid.*, **78**, 6339 (1956).

(4) W. S. Johnson, B. Bannister, R. Pappo and J. E. Pike, *ibid.*, **78**, 6354 (1956).

(5) W. S. Johnson, *ibid.*, **65**, 1317 (1943).




I II III IV V VI

For some time we have been searching for factors that influence the stereochemical course of this reaction, and wish now to disclose a method of control which leads predominantly to the desired *trans* configuration.

Models indicate that replacement of the tetrahedral carbon at certain positions, *e.g.*, $C_7$, of the α-decalone system by a trigonal carbon atom results in elimination of one of the axial hydrogen atoms that hinders *trans* approach to the anion by an electrophilic agent. To test the hypothesis that the stereochemical course of the methylation would thus be favorably influenced, we have examined the α-decalone system with a double bond at 6,7 (formula I), noting that the introduction of the additional trigonal carbon at $C_6$ does not appear to affect the hindrance on either side of the anion. 2-Furfurylidene-$\Delta^6$-octalone-1 (I, R = H, Ar = $C_4H_3O$), m.p. 136–137°, C, 78.6; H, 7.02, prepared from the corresponding octalone,[6] was methylated with potassium *t*-butoxide and methyl iodide.[5] The only pure product that was isolated (in 56% yield) was indeed the desired *trans* compound I (R = $CH_3$, Ar = $C_4H_3O$), m.p. 75.5–76.5°, C, 79.2; H, 7.53. The configuration was proved by alkaline peroxide oxidation[4] followed by hydrogenation of the resulting unsaturated acid to give the known *trans*-2-carboxy-2-methylcyclohexyl-β-propionic acid, identified by comparison with authentic material.[7]

The principle was then applied to a synthesis of *dl*-3β-hydroxy-9,11-dehydroandrostane-17-one (VI). The stereoselective production of the 3β,11β-dihydroxy-18-nor-D-homo ketone II (R = H) already has been described.[3] Treatment with succinic anhydride afforded the half-succinate which, as the methyl ester II (R = $COCH_2CH_2COOCH_3$), m.p. 168.5–169.5° C, 68.5; H, 8.59, was dehydrated with phosphorus oxychloride and pyridine to give the 9,11-dehydro compound III (R = $COCH_2CH_2COOCH_3$), m.p. 126.5–127.5°, C, 71.6; H, 8.48. Saponification followed by condensation with furfural yielded the furfurylidene ketone m.p. 190–191.5, C, 78.8; H, 8.21, and this, on

(6) P. D. Bartlett and G. F. Woods, *ibid.*, **62**, 2933 (1940); *cf.* A. M. Gaddis and L. W. Butz, *ibid.*, **69**, 117 (1947).

(7) W. S. Johnson, *ibid.*, **66**, 215 (1944).

methylation,[8] was converted into the *trans* product IV, m.p. 202–204°, C, 78.9; H, 8.33, in 69% yield. Alkaline peroxide oxidation[4] transformed IV into V (R = H) which was converted with diazomethane into the ester V (R = $CH_3$), and cyclized with potassium *t*-butoxide in benzene.[2] The resulting keto ester was decarbomethoxylated with hydrochloric and acetic acid to give the *dl*-ketone VI, m.p. 158.5–161.5°. The infrared spectrum of this material was indistinguishable from that of authentic 3β-hydroxy-9,11-dehydroandrostane-17-one.[9]

(8) At this stage the 3-hydroxyl group was protected as the tetrahydropyranyl ether (*cf.* ref. 3).

(9) C. W. Shoppee, *J. Chem. Soc.*, 1134 (1946).

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## THE TOTAL SYNTHESIS OF PENICILLIN V

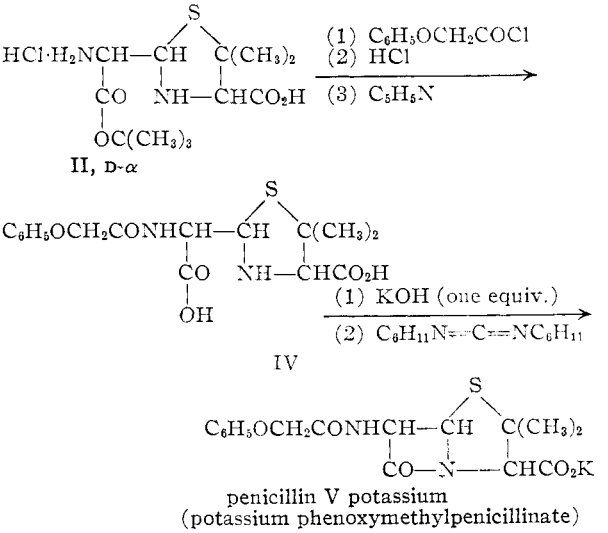
*Sir:*

The ability of aliphatic carbodiimides to form amide bonds in aqueous solution directly from the amine and carboxyl components under very mild conditions[1] suggested the use of these reagents for the cyclization of a pencilloic acid to a penicillin. We have prepared by total synthesis in good overall yield the penicilloic acid corresponding to penicillin V (phenoxymethylpenicillin). By use of N,N′-dicyclohexylcarbodiimide cyclization was effected rapidly at room temperature, thereby completing the first rational synthesis of a natural penicillin.[2]

Condensation of D-penicillamine with *t*-butyl phthalimidomalonaldehydate afforded the *t*-butyl D-α-4-carboxy-5,5-dimethyl-α-phthalimido-2-thiazolidineacetate (I), $C_{20}H_{24}N_2O_6S$, m.p. 161° dec. [Found: C, 57.45; H, 6.06; N, 6.83; $\alpha^{25}D$ + 54° (*c*, 1 in acetic acid)] as described for the corresponding DL-α acid.[3,4] The α, or natural, configuration of the more soluble (ethanol–water) I was established chemically by relationship to natural dimethyl D-α-benzylpenicilloate. The less soluble D-γ-isomer may be isomerized in high yield to the D-α form as in the DL-ester series,[4] thus providing a stereochemically efficient synthesis. Hydrazinolysis of I, followed by acidification with hydrochloric acid, produced *t*-butyl D-α-4-carboxy-5,5-dimethyl-α-amino-2-thiazolidineacetate hydrochloride (II), $C_{12}H_{23}N_2O_4SCl$, in 85% yield; m.p. 172° dec. [Found: C, 43.83; H, 7.18; Cl, 10.87; $\alpha^{25}D$ + 111° (*c*, 1 in methanol)].

Phenoxyacetyl chloride and triethylamine converted II to α-*t*-butyl D-α-phenoxymethylpenicilloate (III), $C_{20}H_{28}N_2O_6S$, in 75% yield; m.p. 120–122° dec. [Found: C, 56.88; H, 6.86; N, 6.59; $\alpha^{25}D$ + 67° (*c*, 1 in methanol)]. Cleavage of the *t*-butyl ester with dry hydrogen chloride, followed by crystallization from acetone–water containing an equivalent of pyridine, led to 75% of D-α-phenoxymethylpenicilloic acid hydrate (IV), $C_{16}H_{20}N_2O_6S\cdot H_2O$; m.p. 129° dec. [Found: C, 49.61; H, 5.77; N, 6.94; $\alpha^{25}D$ + 94° (*c*, 1 in methanol)]. Identity with a sample prepared by saponification of natural penicillin V[5] was established by comparison of m.p., infrared spectra (KBr), optical rotation and mixed m.p.

Treatment with N,N′-dicyclohexylcarbodiimide in dioxane–water (20 min. at 25°) cyclized IV as the monopotassium salt in 10–12% yield. By partition between methyl isobutyl ketone and *p*H 5.5 phosphate buffer (two funnels) the totally synthetic crystalline potassium salt of penicillin V was isolated. The natural and synthetic potassium salts were shown to be identical by microbiological assay,[6] optical rotation [synthetic, $\alpha^{25}D$ + 223° (*c*, 0.2 in water); natural, $\alpha^{25}D$ + 223° (*c*, 0.2 in water); reported,[7] $\alpha^{20}D$ + 223° (*c*, 1 in water)], infrared spectra (KBr), m.p. 263° dec. (reported,[7] 256–260° uncorr.), undepressed upon admixture.




penicillin V potassium
(potassium phenoxymethylpenicillinate)

The same results were obtained using IV derived from natural penicillin V. The entire series also has been carried through starting with DL-penicillamine. The crystalline DL-penicillin V potassium salt showed 51.4% (514μ/mg.) of the bioactivity of natural penicillin V, indicating that L-penicillin V has little, if any, antibiotic activity. Cyclization of the penicilloate also was effected, but in lower yield, by ethoxyacetylene and a ketenimine (pentamethyleneketene cyclohexylimine[8]). It is interesting to note that the entire reaction sequence starting with penicillamine was conducted at or below room temperature.

We are indebted to Bristol Laboratories of Syracuse, N.Y., for financial support, to Merck and Co., Inc., of Rahway, N. J., for the preparation

(1) J. C. Sheehan and G. P. Hess, THIS JOURNAL, **77**, 1067 (1955).

(2) Penicillamine and 2-benzyl-4-methoxymethylene-5-(4)-oxazolone condense to form trace amounts (0.03 to 0.08% by bioassay, 0.008% isolated) of penicillin G (benzylpenicillin). For a recent review of this reaction see Karl Folkers in "Perspectives in Organic Chemistry," Sir Alexander Todd, Editor, Interscience Publishers, Inc., New York, N. Y., 1956, p. 409.

(3) J. C. Sheehan and D. A. Johnson, THIS JOURNAL, **76**, 158 (1954).

(4) J. C. Sheehan and P. A. Cruickshank, *ibid.*, **78**, 3677 (1956).

(5) Kindly furnished by Eli Lilly & Company, Indianapolis, Ind.

(6) Synthetic potassium penicillin V had a potency of 1078 μ/mg. ± 10% (107.8% ± 10%) compared to standard natural penicillin V in a plate diffusion assay carried out under the supervision of Dr. J. Lein, Bristol Laboratories, Syracuse, N. Y.

(7) E. Brandl and H. Margreiter, *Osterr. Chem. Z.*, **55**, 11 (1954).

(8) Directions for the preparation of this ketenimine were furnished by Dr. C. L. Stevens, Wayne University, private communication.