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.

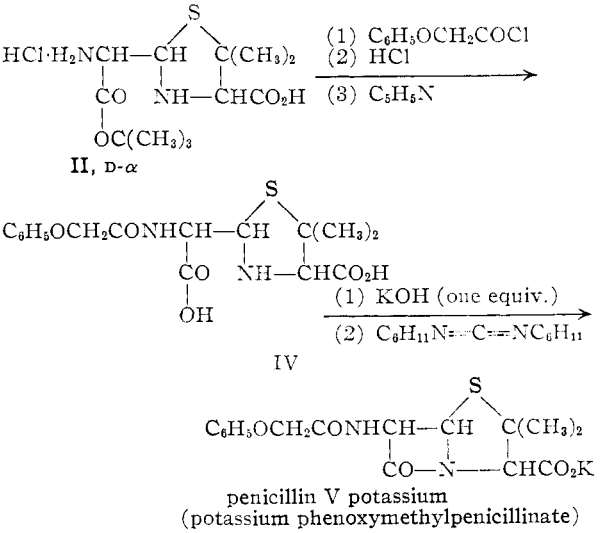
(1) J. C. Sheehan and G. P. Hess, THIS JOURNAL, **77**, 1067 (1955).

(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).

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

(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.

of substantial quantities of certain key intermediates and to Mr. Sergey V. Chodsky for technical assistance.

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THE SALT EFFECT IN THE AROMATIC NUCLEOPHILIC SUBSTITUTION REACTION[1]

Sir:

The effect of added neutral salts upon the velocity of the second order of the ion–dipole aromatic nucleophilic substitution reactions of lithium, sodium and potassium methoxides with 2,4-dinitrochlorobenzene has been investigated at 25°. The rates were studied in absolute methanol solvent as a function of reactant ($LiOCH_3$, $NaOCH_3$, and $KOCH_3$) in the presence of added cations (Li^+, Na^+, and K^+) and added anions ($C_2H_3O_2^-$, I^-, Br^-, ClO_4^-, Cl^-, and NO_3^-). The reaction of $NaOCH_3$ in the presence of added $LiClO_4 \cdot 3H_2O$ also was studied in a 50 volume % methanol-benzene solvent.

For reactions without added salts, the rate constants (1 $mole^{-1}$ $sec.^{-1}$) were: $LiOCH_3$, 0.0242; $NaOCH_3$, 0.0262; $KOCH_3$, 0.0278. A consistent pattern of salt effects is typified by the data for the $LiOCH_3$ reaction shown in Fig. 1. At low concentrations of added salt, each cation exhibits an individual effect, added to that of the cation introduced along with the reactant methoxide. The anions cause an additional secondary effect. The reaction rate increases for acetate > Cl^-, Br^- > I^-, NO_3^- > ClO_4^-. Salt effects are more pronounced in solvents of lower dielectric constant. The observed effects cannot be correlated with changes in ionic strength of the reaction medium as found by Bolto and Miller.[2]

A qualitative explanation of the effect of lithium salts assumes the equilibrium

$$LiOCH_3 \rightleftharpoons Li^+ + {}^-OCH_3$$

The addition of a salt providing Li^+ as a common ion should shift this equilibrium to decrease the concentration of the reactant, OCH_3^-. Since the effective concentration of added Li^+ will depend on the degree to which it remains associated with the added anion, the rate will differ with different added salts. This assumes that the ion pair reacts at a negligible rate compared to that for the ion. A similar interpretation has been used to account for the variation in rate of decarboxylation of trichloroacetic acid.[3] The observed effect of anions on reaction rate thus can be interpreted to suggest that the order of attraction for lithium ions in methanol is Ac^- > Cl^-, Br^- > NO_3^-, I^- > ClO_4^-.

The fact that $NaOCH_3$ and $KOCH_3$ react faster suggests that the corresponding equilibria involving these methoxides is shifted more to the right, providing a greater effective concentration of OCH_3^-. Conductivity data[4] suggest that more ion association occurs for $LiOCH_3$ than for $KOCH_3$ or $NaOCH_3$ in methanol. Potassium salts are strong electrolytes in methanol with dissociation constants of about 0.1 to 0.02.[5] It is known that potassium salts are stronger electrolytes than are lithium salts in acetone.[6] If a similar order of electrolyte strength holds for methanol solutions, then the effect of added potassium salts on the $LiOCH_3 \rightleftharpoons Li^+ + {}^-OCH_3$ equilibrium would be to supply anions which would tend to associate more readily with Li^+ so that the equilibrium would be shifted to provide a greater concentration of OCH_3^-. This accounts for the increase in rate of the reaction. Sodium salts are not as effective as potassium salts, and the anion effects are consistent with those observed in the presence of Li^+ alone.

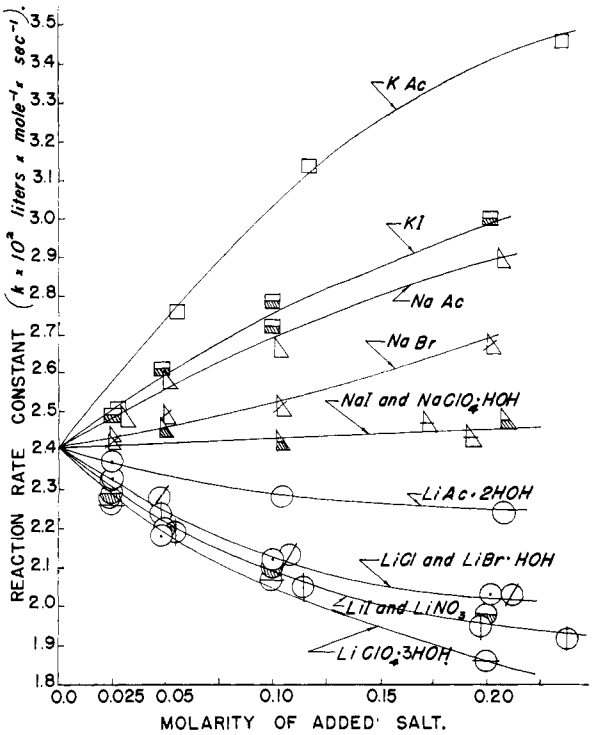

Fig. 1.—Lithium methoxide and 2,4-dinitrochlorobenzene.

(1) This research supported by the Petroleum Research Fund of the American Chemical Society.

(2) B. Bolto and J. Miller, *Australian J. Chem.*, **9**, 74 (1956).

(3) G. A. Hall and F. H. Verhoek, THIS JOURNAL, **69**, 613 (1947).

(4) G. E. M. Jones and O. L. Hughes, *J. Chem. Soc.*, 1197 (1934).

(5) E. C. Evers and A. G. Knox, THIS JOURNAL, **73**, 1739 (1951).

(6) J. F. Dippy, H. O. Jenkins and J. E. Page, *J. Chem. Soc.*, 1368 (1939).

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THE EFFECT OF NITRATE ION ON THE YIELD OF HYDROGEN FROM WATER RADIOLYSIS

Sir:

Solutions of calcium nitrate have been irradiated in the mixed fast neutron-γ-flux of the Harwell experimental reactor BEPO at a temperature of about 80°. Nitrate concentration was varied from 15.9 to 0.037 *M*. The thermal neutron dose was monitored using cobalt wire of high purity.[1] Energy deposition figures were derived using the data of

(1) J. Wright, to be published.