that hydrogen is absorbed at temperatures from 25 to 40° at 1 atm by tetrahydrofuran solutions of sodium naphthalene. Sodium hydride in an exceedingly reactive form is the product of the reaction.

The current study was initiated with the view that in large part the difficulty with the sodium–hydrogen reaction is the protective film of solid sodium hydride covering the sodium.[2] Indeed special means to disperse the sodium improve the yield and lower the required temperature.[3] A successful low-temperature reaction of sodium and hydrogen requires that the sodium be present in a very highly dispersed form and equally important that the reduction potential of the system be sufficient for facile reaction. These requirements suggested the use of sodium naphthalene. Since sodium naphthalene is essentially molecularly dispersed, surface problems are eliminated. Moreover, encouraged by the recent demonstrations of the powerful electron-transfer properties of this reagent,[4,5] we sought to activate molecular hydrogen at moderate temperatures.

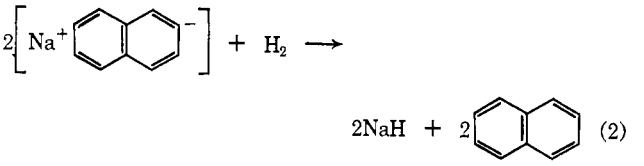
The reaction of sodium naphthalene (50 mmol) in tetrahydrofuran with hydrogen at 40° was conducted using a modified B[2] hydrogen generator.[6] The radical anion solution was prepared under N_2 in a three-necked round-bottom flask in place of the usual hydrogenation flask, and a drying tube was placed between the hydrogen generator and the reaction flask. Reaction was followed both by the uptake of hydrogen and by assaying the radical anion concentration in the reaction vessel.[7] Over a 60-hr period 25 mmol of hydrogen was absorbed and the concentration of radical anion went to zero. The reaction rate is very sensitive to the stirring rate as expected for a two-phase reaction, and, since the magnetically driven glass stirring bar affords only minimal efficiency, we expect shorter reaction times in the more efficiently stirred reactions, which we are presently devising. The solid product was separated by centrifugation and found to be highly pyrophoric. A sample of the solid was allowed to react with water in a gas displacement apparatus to give hydrogen, and the resulting solution was titrated with standard acid. The ratio of H_2:NaOH obtained (0.93) is close to the value of 1.0 required by eq 1. The yield based on H_2 is greater than 90%.

$$NaH + H_2O \longrightarrow H_2 + NaOH \qquad (1)$$

Conclusive evidence that highly active sodium hydride was the product was afforded by quenching the entire reaction mixture directly with deuterium oxide and analyzing the resulting gas by mass spectrometry. In control experiments we have shown that under these conditions sodium metal gives predominantly D_2, and authentic sodium hydride (Metal Hydrides, Inc.) gives predominantly HD. The product of the sodium naphthalene–hydrogen reaction gave predominantly HD (85%),[8] thus confirming that the principal product is indeed sodium hydride, as predicted.

The reaction involves electron transfer, evidenced by the fact that the naphthalene is recovered quantitatively. Our analytical method based on gas chromatography with internal standards would have detected 0.2% dihydronaphthalenes or tetralin, the expected products of naphthalene if sodium naphthalene functioned as a nucleophile in this reaction. Significantly, electron transfer to nitrogen has been observed with sodium naphthalene in the presence of titanium alkoxides.[5]

While the actual scheme probably involves several steps, our results suggest stoichiometric reaction given



(2)

by eq 2. As regards the intervening steps, it is only clear that naphthalene is inert. Of greater interest 1-octene is also inert when present during and after the hydrogenation of sodium naphthalene, and the yield of sodium hydride is unaffected. Further speculation about the mechanism must await the results of experiments in progress.

Not only is the present reaction a more convenient procedure, but it also produces sodium hydride in an exceedingly active form. In preliminary experiments we have observed that it converts cyclohexanone to the enolate rapidly at room temperature. We are presently exploring its use as a catalyst and reagent for a variety of reactions.

Acknowledgment. We gratefully acknowledge support by the National Science Foundation. We especially wish to thank Professor Kevin T. Potts (Rensselaer Polytechnic Institute) for his invaluable assistance in the determination and analysis of the mass spectra.

(3) A. M. Muckenfuss, U. S. Patent 1,958,012 (May 8, 1934).

(4) (a) W. D. Closson, P. Wriede, and S. Bank, *J. Am. Chem. Soc.*, 88, 1581 (1966); (b) G. D. Sargent, J. N. Cron, and S. Bank, *ibid.*, 88, 5363 (1966); (c) S. Ji, L. B. Gortler, A. Waring, A. Battisti, S. Bank, and W. D. Closson, *ibid.*, 89, 5311 (1967).

(5) E. E. van Tamelen, G. Boche, and R. Greeley, *ibid.*, 90, 1677 (1968).

(6) C. A. Brown and H. C. Brown, *J. Org. Chem.*, 31, 3990 (1966).

(7) A 1-ml sample of the radical anion solution is quenched in 5 ml of water containing 0.5 ml of benzene. A sample of the benzene layer is then analyzed by gas chromatography (4-ft Carbowax 20M at 140°) for dihydronaphthalenes and naphthalene. Since it is known that 1 mol of sodium naphthalene produces 0.5 mol of dihydronaphthalene, the amount of dihydronaphthalene is then one-half the concentration of the radical anion.

(8) The residual gases were H_2 and D_2. Entirely analogous results were obtained by Wender, Friedel, and Orchin with sodium hydride and heavy water: I. Wender, R. A. Friedel, and M. Orchin, *J. Am. Chem. Soc.*, 71, 1140 (1949).

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Studies on Lactams. X.[1] Total Synthesis of 5,6-*trans*-Penicillin V Methyl Ester

Sir:

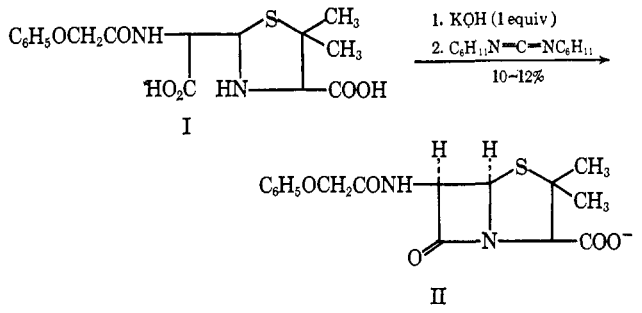
Intensive cooperative research in the United Kingdom and the United States during World War II led to the unequivocal determination of the structure and stereochemistry of penicillin,[2] but it was not until 1957 that an elegant total synthesis[3] of the antibiotic was achieved.

(1) (a) Presented before the 5th International Symposium on the Chemistry of Natural Products, London, July 1968. (b) For part IX, see A. K. Bose, G. Spiegelman, and M. S. Manhas, *Chem. Commun.*, 321 (1968).

(2) H. T. Clarke, J. R. Johnson, and R. Robinson, "The Chemistry of Penicillin," Princeton University Press, Princeton, N. J., 1949.

(3) J. C. Sheehan and K. R. Henery-Logan, *J. Am. Chem. Soc.*, 79, 1262 (1957); 81, 3089, 5838 (1959).

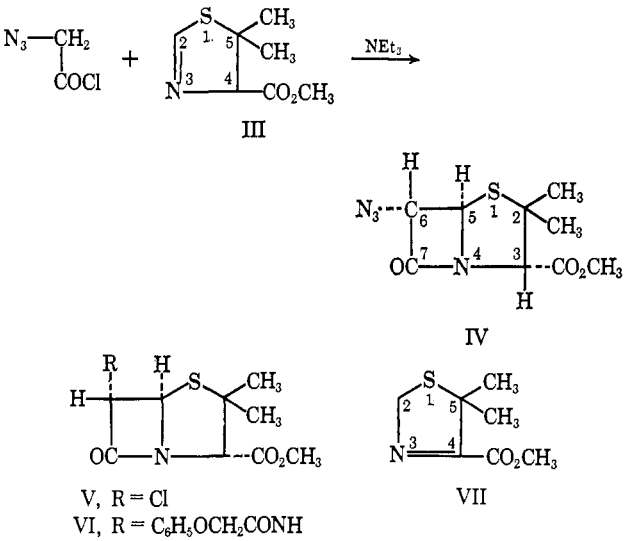
In this synthesis the formation of the scission-prone β-lactam ring was postponed until the very end of the synthetic operations. The key reaction in this scheme was the cyclization of a suitably substituted D-α-phenoxypenicilloic acid (I) to the penam derivative II with the help of dicyclohexylcarbodiimide. More recently ingenious approaches[4,5] to the penicillin structure have been described,[4,5] but no new total synthesis has been disclosed.



In this communication we wish to report an extension of our method[6,7] for the preparation of 3-azido-2-azetidinones to the synthesis of the title compound. The use of the azido group as the progenitor of the amide side chain in penicillin was expected to permit the construction of the β-lactam ring at an early stage of the synthesis since the subsequent steps planned were not likely to be inimical to this ring system.

Methyl 5,5-dimethyl-2-thiazoline-4-carboxylate[8] (III), mp 28–31°, was prepared[9] in one step by heating (±)-N-formylpenicillamine[2] with boron trifluoride etherate in methanol solution. The location of the imine double bond was indicated by its nmr spectrum which displayed singlets at τ 8.68 (3 H), 8.27 (3 H), and 6.19 (3 H) for the methyl groups and an AB pattern (J = 2.5 cps) with doublets centered at τ 5.38 (1 H) and 1.90 (1 H). The isomeric 3-thiazoline structure VII is incompatible with the chemical shift of τ 1.90 for one of the methylene protons at C-2 and a geminal coupling constant of 2.5 cps.

The reaction between III and azidoacetyl chloride in the presence of triethylamine was examined under various conditions and found to be extremely sensitive to moisture. After rigorous exclusion of moisture, reproducible yields (5–8%) of the desired bicyclic β-lactam IV could be obtained when triethylamine was added under high dilution conditions to a refluxing methylene chloride solution of III and azido acid chloride. Repeated chromatography over Florisil (100–200 mesh)[10] followed by low-temperature crystallization led to pure IV,[8] mp 39–41°, which was characterized by ir bands at 4.70, 5.61, and 5.72 μ. The mass spectrum, which was recorded using a heated inlet system, failed to show the molecular ion, but $(M - N_2)^+$ and other fragments expected for IV were observed. In addition to supporting the gross structure, the nmr spectrum of IV also revealed the stereochemistry. The size of the coupling (J = 1.5 cps) between protons at C_5 and C_6 was indicative of 5,6-*trans* stereochemistry.[7,11]



In a recent investigation,[12] natural 6-aminopenicillanic acid was converted to 6-chloropenicillanic methyl ester (V) by diazotization in the presence of hydrochloric acid followed by esterification with diazomethane. These reactions should leave the configuration at C_3 and C_5 unchanged (*i.e.*, C_3–C_5 *trans* as in penicillin). The protons at C_5 and C_6 in V are *trans* because of a coupling of 2 cps between them. The nmr spectrum of V is virtually identical with that of IV except for the position of the C_6–H signal. Since the chemical shift of C_3–H can be expected to be modified by the relative configuration at C_3 and C_5,[13] the identity of the chemical shift of the C_3 protons in IV and V is strongly indicative of C_3–C_5 *trans* geometry in IV. Therefore, in all probability IV can be described as 6-epiazidopenicillanic acid methyl ester.

Catalytic reduction of IV in ethyl acetate solution with hydrogen in the presence of Adams catalyst showed that the catalyst was being poisoned. When an excess of catalyst was used, scission of the β-lactam ring appeared to be competitive with the reduction of the azide group. However, with benzene as solvent and an excess of Adams catalyst, the desired 6-aminopenicillanic ester could be produced in moderate yield. The impure amino-β-lactam so obtained was used directly for acylation with phenoxyacetyl chloride in the presence of triethylamine, and the product was chromatographed and recrystallized to give an amido ester[8] (VI), mp 151–152°, in about 17% yield[14] based on the azide IV. The ir and nmr spectra of VI were fully in accord with the structure and stereochemistry of the desired 6-epipenicillin V methyl ester.

Very recently the isomerization of natural 6-aminopenicillanic acid to certain *trans* derivatives has been reported.[15,16]

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(5) E. J. Corey and A. M. Felix, *J. Am. Chem. Soc.*, 87, 2518 (1965).
(6) A. K. Bose and B. Anjaneyulu, *Chem. Ind.* (London), 903 (1966).
(7) A. K. Bose, B. Anjaneyulu, S. K. Bhattacharya, and M. S. Manhas, *Tetrahedron*, 23, 4769 (1967).
(8) Satisfactory elemental analysis was obtained for this compound.
(9) We are indebted to Professor S. Wolfe, Queens University, Kingston, Ontario, Canada, for this convenient procedure. We had found earlier that III can be obtained in low yield by the condensation of penicillamine methyl ester with ethyl N-phenylformimidate.
(10) Available from Fischer Scientific Co.
(11) J. L. Luche, H. K. Kagan, R. Parthasarathy, G. Tsoucaris, C. de Rango, and C. Zelwer, *Tetrahedron*, 24, 1275 (1967).
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(14) The conditions for optimum yields have not been determined for the various steps of our synthesis.
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(16) D. A. Johnson, D. Mania, C. A. Panetta, and H. H. Silvestri, *Tetrahedron Letters*, 1903 (1968).

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(17) NASA Trainee during 1964–1967.

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A New Method for the Removal of Chloroacetyl Groups

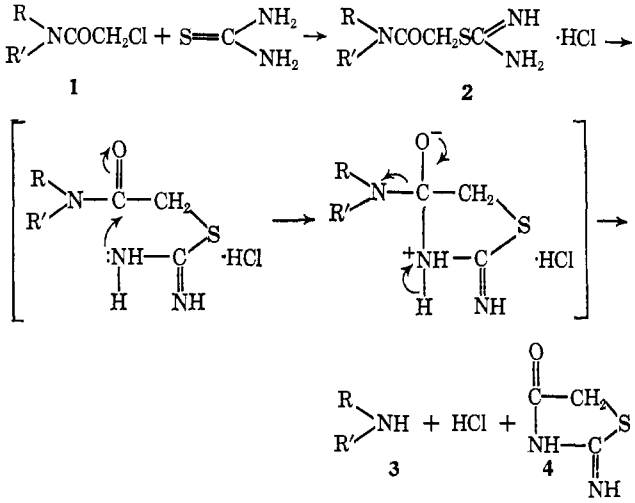
Sir:

Several methods have been known for the fission of the amide bond in chloroacetylamines. The hydrolytic fission can be effected in 10 *N* hydrochloric acid–glacial acetic acid[1] or in alcoholic hydrogen chloride.[2] Holley and Holley[3] reported an intramolecular aminolysis method which consisted in the treatment of chloroacetyl peptides with *o*-phenylenediamine in aqueous lithium hydroxide at 100°.

In this paper, we wish to report a new and milder method for the removal of chloroacetyl group from the compounds including it as a protecting group of amines.

Recently, we found that the reaction of 1-chloro-2-oximino-3-butanone or 2-bromoacetophenone oxime with thiourea led to the formation of 4-(1-oximinoethyl)- or 4-phenyl-2-aminothiazole.[4] In an extension of this reaction, it was envisaged that reacting chloroacetylamine **1** with thiourea would result in the initial formation of the S-substituted thioformamidine hydrochloride **2**, which would then undergo the intramolecular amidinolysis to liberate the corresponding amine **3** with the concomitant formation of pseudothiohydantoin **4**, as illustrated in Scheme I.

Scheme I



Thus, N-chloroacetyl-*p*-nitroaniline was treated with 1 equiv of thiourea in ethanol, giving S-(*p*-nitrophenylcarbamoylmethyl)thioformamidine hydrochloride[5] in 85% yield. When the amidine was heated in an aqueous solution for 15 min, *p*-nitroaniline was, as expected, obtained in 88% yield, together with a 71% yield of pseudothiohydantoin hydrochloride.

In analogous treatment of N-chloroacetyl-N′-formylpiperazine with thiourea, the selective removal of the chloroacetyl group was effected, and N-formylpiperazine was quantitatively liberated as the hydrochloride. The reaction was examined on a variety of chloroacetylamines, and the liberated amines were isolated in a yield between 69 and 84%, as shown in Table I.

Table I. Yields of the Reaction Products

Chloroacetylamine **1** R	R′	Products: Amine **3**	Yield,[a] %	Yield of **4**,[a] %
p-$NO_2C_6H_4$–	H–	*p*-Nitroaniline	75	60
p-$CH_3OC_6H_4$–	H–	*p*-Anisidine	75	78
$ClCH_2CON$ N–		Piperazine	84[b]	76
$OHCN$ N–		N-Formylpiperazine	77[c]	76
$C_6H_5CH_2$ | $C_6H_5NHCOCH$–	H–	Phenylalanylaniline	69	66
$HOOCCH_2NHCOCH_2$–	H–	Glycylglycine	75[d]	67

[a] All yields were calculated from the chloroacetylamine **1**. [b] The yield was based on conversion into the picrate. [c] The yield was based on conversion into the N′-tosyl derivative, mp 143.8–144.5°.[5] [d] The yield was of the hydrochloride monohydrate.

The advantages of this method are as follows. (1) The selective removal of the chloroacetyl group is possible, as illustrated in the cases of N-chloroacetyl-N′-formylpiperazine, chloroacetylphenylalanylaniline, and chloroacetylglycylglycine, since the reaction can be carried out under mild conditions, where the other usual amide bonds cannot be hydrolyzed. (2) The reaction is effected in a medium having an acidity based on thioformamidine hydrochloride and/or amine hydrochlorides during the entire reaction time, while Holley and Holley's method[3] using *o*-phenylenediamine is performed in the presence of lithium hydroxide. (3) Separation of products is not difficult, since the bulk of pseudothiohydantoin crystallizes out when the reaction mixture is cooled, while the liberated amines remain usually as the hydrochloride in aqueous solution.[6]

The following procedure is representative, but some variations should be made mainly in reaction time according to the compounds used. A suspension of chloroacetylglycylglycine (2.09 g, 0.01 mol) and thiourea (95%, 0.80 g, 0.01 mol) in ethanol (30 ml) was heated at 60–65° for 1 hr, and the resultant solution was refluxed for 40 min. The ethanol was removed by rotary evaporation, and water (14 ml) was added to the crystal-

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(4) M. Masaki, M. Sugiyama, S. Tayama, and M. Ohta, *Bull. Chem. Soc. Japan*, **39**, 2745 (1966).
(5) A satisfactory elemental analytical result was obtained for this new compound.
(6) In general, the basicity of pseudothiohydantoin is weaker than that of the liberated amines. However, *p*-nitroaniline is a weaker base than pseudothiohydantoin; thus the former was liberated as the free base. See the following references for the basicity of pseudothiohydantoin: (a) E. V. Vladzimirs'ka and Yu. M. Pashkevich, *Zh. Obshch. Khim.*, **33**, 3149 (1963); (b) M.-L. Girard and C. Dreux, *Compt. Rend.*, **260**, 2225 (1965).