of the acetate of 2-phenylethanol (compound 16), however (where the distance of the complexed TTFA from the ring has been increased; *i.e.*, $-O(H) \cdots TTFA \rightarrow$ $-OC(CH_3)=O\cdots TTFA)$, results in predominantly para substitution (84 %).

Since arylthallium ditrifluoroacetates are versatile synthetic intermediates for the preparation of phenols,¹¹ thiophenols,¹² and nitriles,¹¹ as well as iodides,⁴ control over the orientation of the thallation reaction, as demonstrated in the examples given above, has as its consequence control over isomer distribution in a spectrum of aromatic substitution reactions.

(11) E. C. Taylor, H. W. Altland, R. H. Danforth, G. McGillivray, and A. McKillop, to be published.

(12) E. C. Taylor, M. Ochiai, and A. McKillop, to be published. (13) NRCC Postdoctoral Fellow, 1968-1970.

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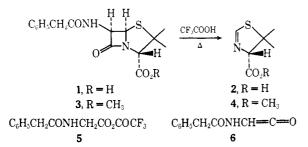
> > Alexander McKillop

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Degradation of Penicillin G Methyl Ester and Penillonic Acid Methyl Ester to D-5,5-Dimethyl- Δ^2 -thiazoline-4-carboxylic Acid Methyl Ester

Sir:

We wish to report a new and potentially useful chemical degradation of penicillin G (1). A solution of 1 in trifluoroacetic acid which had been heated at the boiling point exhibited nmr signals¹ at δ 1.75 (s, 3), 2.0 (s, 3), 5.35 (d, 1, J = 2 Hz), and 9.6 ppm (d, 1, J= 2 Hz) which are characteristic of 5,5-dimethyl- Δ^2 thiazoline-4-carboxylic (2).² To acid facilitate



isolation of the thiazoline the degradation was performed on the methyl ester 3.³

A 10% solution of compound 3 in CF₃COOH was heated at reflux for 15 min and evaporated in vacuo at room temperature. The residue was dissolved in methylene chloride and quenched with excess aqueous ammonia. Evaporation and distillation of the dried methylene chloride solution afforded a 50-60% yield of optically active thiazoline 4 [mp

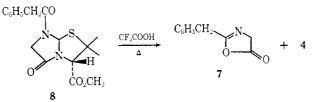
(2) H. M. Crooks, Jr., in "The Chemistry of Penicillin," H. T. Clarke, J. R. Johnson, and R. Robinson, Ed., Princeton University Press, 1949, p 471.

(3) Prepared in 96% yield by methylation of potassium penicillin G with methyl iodide in dimethylformamide solution.

50.5-51.5°; $[\alpha]^{25}D$ +51.9° (c 1, CHCl₃); lit.⁴ mp 50°]. A solution infrared spectrum of this compound was identical with that of authentic racemic thiazoline.⁵ The optical integrity of the carbon atom bearing the carbomethoxy group appears to have been preserved since the melting point of the thiazoline is the same as that reported for the thiazoline prepared from D-penicillamine.⁴ Hydrolysis of compound 4 with hot 2 NHCl gave D-penicillamine hydrochloride [mp 177-179.5° dec; $[\alpha]^{25}D - 49.8^{\circ}$ (c 1, 1 N NaOH)]⁶ in 70% yield.

Although the precise fate of the N-phenylacetylglycyl fragment of 3 is not known, addition of the reaction mixture to an excess of benzylamine in pyridine led to the isolation of the benzylamide of N-phenylacetylglycine in 27 % yield.⁷ Formation of this product supports the view that the N-phenylacetylglycyl fragment is present in CF₃COOH as the mixed anhydride 5,8 the acylamino ketene 6,9 or the benzyloxazolone 7.¹⁰ The absence of nmr signals characteristic of oxazolone 7 and the stability of 7¹¹ in CF₃COOH apparently eliminate the oxazolone as a final product in the CF₃COOH degradation of penicillin G.

However, when penillonic acid methyl ester $(8)^{12}$ was heated in CF3COOH a clean conversion to oxazolone 7 and thiazoline 4 occurred. The nmr spectrum of the reaction mixture approximated that of equal parts of authentic 4 and 7. Optically active 4 was isolated and the N-phenylacetylglycyl fragment was



characterized as the benzylamide derivative. Jansen and Robinson¹⁰ reported the reverse reaction, 4 + 7 \rightarrow 8, occurs in benzene solution. Furthermore, they suggested that the penillonic acid rearrangement proceeds by dissociation of penicillin to 4 and 7 followed by recombination to 8. The degradation of penicillin

(4) Merck Report No. 63, p 18, April 1945, cited in ref 2, p 1057.
(5) A. K. Bose, G. Spiegelman, and M. S. Manhas, J. Amer. Chem. Soc., 90, 4506 (1968). These workers reported that DL-4 could be prepared by heating DL-N-formylpenicillamine with boron trifluoride etherate in methanol. Prior to their publication we had synthesized DL-4 by hydrogen chloride catalyzed esterification of DL-2 in the presence of trimethyl orthoformate. The Merck group⁴ prepared D-4 by the reaction of ethyl formimidate hydrochloride and D-penicillamine methyl ester.

(6) An authentic sample of D-penicillamine hydrochloride (Aldrich Chemical Co.) had $[\alpha]^{25}D = 50.6^{\circ}$ (c 1, 1 N NaOH); "The Merck Index," P. G. Stecher, Ed., Merck and Co., Rahway, N. J., 1968, p 789, reports mp 177.5° dec; $[\alpha]^{25}D - 55^{\circ}$ (c 1, 1 N NaOH).

(7) R. L. Peck and K. Folkers in ref 2, p 190.

(8) E. J. Bourne, S. H. Henry, C. E. M. Tatlow, and J. C. Tatlow, J. Chem. Soc., 4014 (1952), have shown that mixed anhydrides of carboxylic acids and trifluoroacetic acid react with primary amines to produce a mixture of amides.(9) W. O. Godtfredsen, W. von Daehne, and S. Vangedal, *Experi-*

entia, 23, 280 (1967), suggest an aminoketene or its equivalent to account for the products observed upon irradiation of an aqueous solution of 6-aminopenicillanic acid.

(10) A. B. A. Jansen and R. Robinson, Monatsh. Chem., 98, 1017 (1967). A more convenient procedure than that reported for the preparation of 7 is the treatment of phenylacetylglycine with dicyclohexylcarbodiimide in methylene chloride solution.

(11) The nmr spectrum of authentic 2-benzyl-5-oxazolone (7) in CF₃COOH is essentially unchanged after heating at reflux for 15 min. (12) R. L. Peck and K. Folkers in ref 2, p 188.

⁽¹⁾ Nuclear magnetic resonance (nmr) spectra were measured on a Varian A-60 spectrophotometer using $(CH_3)_4Si$ as internal standard. Optical rotations were measured on a Rudolph 137 polarimeter. In-frared spectra were measured on a Perkin-Elmer 257 grating infrared spectrophotometer. Melting points are uncorrected.

to **4** provides support for the first step of the proposed pathway.¹³

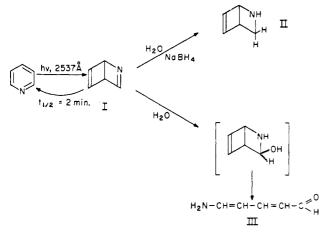
(13) Possible mechanisms for the CF $_3$ COOH transformations will be discussed in our full paper.

Malcolm R. Bell, John A. Carlson, Rudolf Oesterlin Sterling-Winthrop Research Institute Rensselaer, New York 12144 Received February 2, 1970

Photochemistry of Nitrogen Heterocycles. Dewar Pyridine and Its Intermediacy in Photoreduction and Photohydration of Pyridine¹

Sir:

We wish to report (1) that photoisomerization of pyridine to a Dewar pyridine, 2-azabicyclo[2.2.0]hexa-2,5-diene (I), occurs in the liquid phase at 2537 Å; (2) that photoreduction of pyridine occurs in aqueous sodium borohydride, yielding 2-azabicyclo[2.2.0]hex-5ene (II), and (3) that I is an intermediate in the formation of II, as well as in the photohydration² of pyridine to 5-amino-2,4-pentadienal (III). The Dewar pyridine, which is the first valence isomer of pyridine or its derivatives to be found,³ reverts completely to pyridine within 15 min at room temperature, but fortunately has a high activation energy, 16 kcal mol⁻¹, for rearomatization. The picolines and several lutidines also form thermally unstable photoisomers which are reduced by borohydride and hydrolyzed by water.



The formation and rearomatization of these photoisomers can be observed spectrophotometrically. The uv absorption of a $2.5 \times 10^{-4} M$ solution of pyridine in acetonitrile receiving 2.4×10^{17} g cm⁻² min⁻¹ at 2537 Å decreases 7% in a 1-min irradiation and is restored quantitatively in the dark with a half-time of 2.5 min at 25°. (The rates of formation and decay of methylpyridine photoisomers are of the same magnitude.) The limiting concentration of I, 14%, reached upon further irradiation is lower than that expected in the absence of photochemical disappearance, suggesting

(5) E. C. Taylor and R. O. Kan, ibid., 85, 776 (1963).

that the calculated quantum yield of 0.05 may be lower than the true value (vide infra). At 0°, the Dewar pyridine is formed at a comparable rate but has a considerably longer half-life, 36 min. Its uv spectrum at this temperature, measured against a pyridine blank, shows only end absorption, $E_{2200} \simeq 4000$.

The thermal and photochemical properties of I permit accumulation of moderate quantities in photolyses at low temperatures. An amount sufficient for nmr analysis was prepared by irradiating 50 mg of pyridine in 35 ml of *n*-butane for 45 min at -15° with a G8T5 germicidal lamp. The reaction mixture was processed by adding 300 mg of pyridine- d_5 , removing solvent at -50° , and distilling the pyridine solution of I at -30° . In addition to the pyridine resonances, the nmr spectrum⁶ at -25° showed four multiplets of equal area at δ 4.03, 5.22, 6.51, and 6.54. These resonances were absent after the sample had been maintained at 25° for 15 min. On the basis of their chemical shifts and coupling constants⁷ they have been assigned to protons at positions 4, 1, 6, and 5, respectively. The resonance of the proton at position 3, indicated by the multiplicities of those at positions 1 and 4, would be expected to fall at lower field and be obscured by the large pyridine resonances.

When pyridine is irradiated at 2537 Å in aqueous NaBH₄ it disappears with a quantum yield of 0.07 and is not regenerated thermally. The initial product⁸ of such irradiations, extracted into ether, has an elution volume 0.7 that of pyridine on a Carbowax 20M (3%)–polyethylenimine (1.7%) column⁹ at 70° and a parent mass of 81. It has been isolated by preparative glpc and identified as 2-azabicyclo[2.2.0]hex-5-ene (II) by its nmr spectrum and by its reduction with P-1 nickel boride catalyst¹⁰ to cyclobutanemethylamine¹¹ and piperidine. The nmr spectrum of II in CCl₄ shows a singlet (N–H) at δ 1.22 and multiplets at δ 2.93, 3.36, 3.51, 4.28, 6.32, and 6.51. These have been assigned¹² to protons at positions 3-endo, 4, 3-exo, 1, 5, and 6. respectively.

Photolysis of 3,5-lutidine in aqueous NaBH₄ yields a corresponding dihydro product, 4,6-dimethyl-2-azabicyclo[2.2.0]hex-5-ene. Its nmr spectrum shows singlets at δ 1.15 (N-H) and 1.20 (4-CH₃) and multiplets at δ 1.76 (6-CH₃), 3.02 (3_n), 3.21 (3_x), 3.76 (1), and 6.07 (5).

The intermediacy of I in the formation of II was shown by the fact that II was found when an aliquot of a briefly irradiated ether solution of pyridine was stirred with aqueous $NaBH_4$ immediately after irradiation, but was absent when another aliquot was similarly treated 10 min later.

Previous studies have shown that irradiation of aqueous pyridine at 2537 Å yields a product which

(6) Nmr spectra were taken at 100 Mc on a Varian HA-100 spectrometer. We are indebted to Mrs. Gail Ryan for these spectra.

(7) $J_{1,4} \simeq J_{1,5} \simeq J_{5,6} = 1.7 \text{ cps}; \ J_{1,3} \simeq J_{1,5} \simeq J_{3,4} = 0.7 \text{ cps}.$

(8) In irradiations continued to the virtual absence of pyridine an equal yield of 1,2,3,6-tetrahydropyridine and a small amount of piperidine are also found.

(9) J. R. L. Smith and D. J. Waddington, J. Chromatog., 42, 183 (1969).

(10) H. C. Brown and C. A. Brown, J. Amer. Chem. Soc., 85, 1005 (1963).

(11) Characterized by identity of glpc retentions and nmr spectrum with those of a sample prepared by reduction of cyclobutanecarbox-amide with LiAlH₄.

(12) Relevant coupling constants in cps are: $J_{1,4} = J_{5,6} = 2.6$; $J_{3n,4} = 2.2$; $J_{3x,4} = 7$; $J_{3n,3x} = 8$. The nmr spectrum of the dihydro product from pyridine-ds shows only three singlets in the ratio of 2:1:1 at δ 1.20, 2.89, and 3.52, respectively.

⁽¹⁾ Based on work performed under the auspices of the U. S. Atomic Energy Commission.

^{(2) (}a) H. Freytag, *Chem. Ber.*, **69B**, 32 (1936), and references therein; (b) D. Abelson, E. Parthé, K. W. Lee, and A. Boyle, *Biochem. J.*, **96**, 840 (1965); (c) J. Joussot-Dubien and J. Houdard-Pereyre, *Bull. Soc. Chim. Fr.*, 2619 (1969).

⁽³⁾ A photoproduct of 2-amino-5-chloropyridine was reported⁴ to be a Dewar isomer, but was subsequently shown⁵ to be a 1,4 dimer.

⁽⁴⁾ E. C. Taylor, W. W. Paudler, and I. Kuntz, J. Amer. Chem. Soc., 83, 2967 (1961).