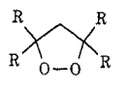
TABLE I
KINETIC DATA FOR THE THERMOLYSIS OF 1,2-DIOXOLANES IN BENZENE[a]



7

	T, (°K)	$k \times 10^5$ (sec^{-1})[b]	$\Delta H^{\pm}$ (kcal/mol)	$\Delta S^{\pm}$ (gibbs/mol)	$\Delta G^{\pm}$ at 500° K (kcal/mol)
	463.2	0.553 ± 0.014			
7b (R = Me)	473.2	1.17 ± 0.06	27.0 ± 0.3	−24.8 ± 0.7	34.4 ± 0.3
	491.2	3.20 ± 0.15			
	463.2	9.04 ± 0.5			
7c (R = Ph)	472.7	15.0 ± 0.6	21.7 ± 0.5	−30.8 ± 2.2	37.1 ± 0.5
	492.2	39.0 ± 2.8			

[a] Error limits have been assessed by least-squares analysis of the rate data employing an IBM computer. [b] Averaged over several runs!

3 served as precursor to rearrangement ketones **6** (eq 1).[3-5]

Of course, this stereochemical result cannot decide whether the 1,3 diradical **2a** is formed from **7a** *via* direct deketonation or whether first simply the peroxide bond in **7a** cleaves to give a 1,5 diradical similar to **3**, which after loss of ketone results in the 1,3 diradical **2a**. For this purpose we examined the kinetics of the thermolysis of 3,3,5,5-tetramethyl- and 3,3,5,5-tetraphenyl-1,2-dioxolanes **7b** and **7c**, respectively, to see whether $\Delta H^{\pm}$ and $\Delta S^{\pm}$ exhibit a dependence on structure.[14] The appearance of carbonyl product was monitored by ir and in all runs good first-order rates were obtained for at least two half-lives. The data is summarized in Table I. Furthermore, it was shown that the rate of acetone production from **7b** is identical within experimental error in C_6H_6 and CH_3CN. No doubt a homolytic fission of the peroxide bond is involved and a structure-reactivity dependence is clearly evident; *i.e.*, benzophenone as leaving group in **7c** helps to lower the activation enthalpy compared to acetone in **7b**, but a considerable price must be paid in the activation entropy, implying a two-bond homolysis and thus direct ketone expulsion (eq 2). However, the activation parameters themselves are rather unexpected, particularly the very negative $\Delta S^{\pm}$ values, and need further comment.

For comparison, the values for di-*tert*-butyl peroxide are $\Delta H^{\pm}$ = 37.8 kcal/mol, $\Delta S^{\pm}$ = +13.8 gibbs/mol, and $\Delta G^{\pm}$ (500°K) = 31 kcal/mol,[15] revealing that the cyclic analog **7b** is by a factor $\sim 3 \times 10^3$ more stable toward thermolysis than di-*tert*-butyl peroxide. The significantly lower $\Delta H^{\pm}$ for the cyclic peroxide **7b** compared with the acyclic analog is not unreasonable since conformational constraint on the oxygen lone pairs is expected to yield a weaker peroxide bond.[16] However, the $\Delta S^{\pm}$ values are without parallel for unimolecular decompositions and certainly cannot be rationalized in terms of two-bond homolysis alone. Excepting the possibility of reduced transmission coefficients in the Eyring equation, possible factors contributing to these unusual $\Delta S^{\pm}$ values might be (a) a high rate of reclosure of 1,5 diradicals, implying that its deketonation is rate determining, (b) a need of selective twisting skeletal deformations in unzipping the ketone leaving group *via* two-bond homolysis in **7**, and (c) an unusually low rotational entropy for the 1-oxatrimethylene diradicals. In the absence of additionally needed experimental data, at this moment we cannot make any commitments as to which of the above factors contributes predominantly to the very negative activation entropies in the deketonation of 1,2-dioxolanes **7**.

(14) P. D. Bartlett and R. Hiatt, *J. Amer. Chem. Soc.*, **80**, 1398 (1958).
(15) W. A. Pryor, "Free Radicals," McGraw-Hill, New York, N. Y., 1966, p 51.
(16) C. W. Gillies and R. L. Kuczkowski, *J. Amer. Chem. Soc.*, **94**, 6337 (1972).

Acknowledgments.—We gratefully appreciate financial assistance of this work by the Donors of the Petroleum Research Fund, administrated by the American Chemical Society, and the National Science Foundation.

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RECEIVED SEPTEMBER 9, 1972

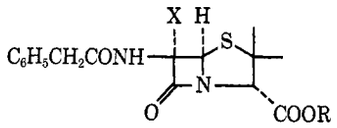
Functionalization of Penicillins at Carbon 6 *via* *N*-Acylimines. 6-Hydroxypenicillin. Substituted Penicillins and Cephalosporins. VIII[1]

Summary: Introduction of 6α-hydroxy, methoxy, benzyloxy, and formyloxy into penicillin G benzyl ester (**2e**) has been achieved by the addition of the appropriate hydroxy compound to the *N*-acylimine **6**, prepared from **2e** by halogenation and elimination.

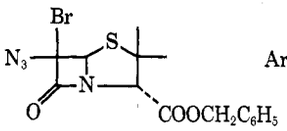
Sir: The finding that a 6(7)α-methoxy group confers β-lactamase stability on penicillins and cephalosporins[2] has stimulated a search for synthetic methods of introducing this and other groups. Particularly sought was 6α-hydroxypenicillin (**1a**) since its antimicrobial activity might be different from that of 6α-methoxypenicillin (**1b**), whose potency is lower than that of the parent, penicillin G (**1e**).[3]

Substituents of many kinds can be introduced into penicillins and cephalosporins at C-6(7) by the addition of nucleophiles to the geminal bromo azide **3**.[3] Similarly, electrophilic reagents react at that position with a carbanion which is stabilized by being adjacent to both the β-lactam carbonyl and an azomethine double bond built on the C-6(7)-amino group.[4] Thus, compounds **4**

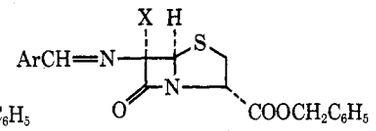
(1) Paper VII: L. D. Cama and B. G. Christensen, *Tetrahedron Lett.*, submitted for publication.
(2) E. O. Stapley, M. Jackson, S. Hernandez, S. B. Zimmerman, S. A. Currie, S. Mochales, J. M. Mata, H. B. Woodruff, and D. Hendlin, *Antimicrob. Ag. Chemother.*, **2**, 122 (1972); T. W. Miller, R. T. Goegelman, R. G. Weston, I. Putter, and F. F. Wolf, *ibid.*, 132 (1972); A. K. Miller, E. Celozzi, B. A. Pelak, E. O. Stapley, and D. Hendlin, *ibid.*, 281 (1972).
(3) L. D. Cama, W. J. Leanza, T. R. Beattie, and B. G. Christensen, *J. Amer. Chem. Soc.*, **94**, 1408 (1972).
(4) R. Reiner and P. Zeller, *Helv. Chim. Acta.*, **51**, 1905 (1968); E. H. W. Böhme, H. E. Applegate, B. Toeplitz, J. E. Dolfini, and J. Z. Gougoutas, *J. Amer. Chem. Soc.*, **93**, 4324 (1971); R. A. Firestone, N. Schelechow, D. B. R. Johnston, and B. G. Christensen, *Tetrahedron Lett.*, 375 (1972); W. A. Spitzer, T. Goodson, R. J. Smithey, and I. G. Wright, *Chem. Commun.* 1139 (1972); D. B. R. Johnston, S. M. Schmitt, R. A. Firestone, and B. G. Christensen, *Tetrahedron Lett.*, 4917 (1972).



1, R = Na
2, R = $CH_2C_6H_5$
1,2a X = OH
b X = OCH_3
c X = OCHO
d X = $OCH_2C_6H_5$
e X = H



3



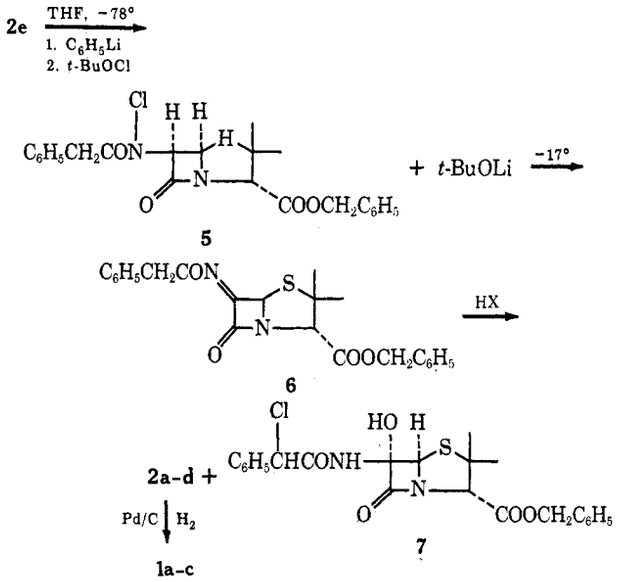
4

have been prepared in which X is alkyl,[4] hydroxyalkyl,[4] Br,[1] and (by exchange with Br) OCH_3,[1] F,[5] N_3,[5] and NC.[5]

When X is a good leaving group, however, the yields of N-acylated penicillins **2** are sometimes poor because X is easily lost during reduction of the azide or hydrolysis of the Schiff base.[1,3,4] Since electronegative 6 substituents become stabilized once the amino group is acylated, a method was sought for their introduction into the intact penicillin G benzyl ester molecule (**2e**).

This was achieved by the method depicted in the Scheme I. Treatment of **2e** (0.25 mmol) in 5 ml of

SCHEME I



THF with PhLi (0.25 mmol) at −78° under N_2 afforded the *N*-lithio derivative, which was chlorinated to **5** at −78° with 35λ *tert*-butyl hypochlorite (0.29 mmol). The by-product, lithium *tert*-butoxide, effected dehydrohalogenation of **5** during warming to −17°, producing *N*-acylimine **6**, benzyl 6-(*N*-phenylacetyl)iminopenicillanate, the key intermediate.[6] Conjugation of the azomethine linkage with the exocyclic carbonyl was expected to confer electrophilic nature on C-6, and attack on the planar site from the less hindered α direction was anticipated.

Addition of 1 ml of methanol at −17° afforded, after chromatography on silica gel with 4:1 $CHCl_3$–EtOAc, 6α-methoxypenicillin G benzyl ester (**2b**), identical with an authentic sample[3] and different from its 6 epimer. Similarly, with water there was obtained the 6α-hydroxy derivative **2a**: ir (μ) 2.9, 5.63, 5.72, 5.92; nmr (δ, $CDCl_3$) 4.37 (s, 3-H), 5.47 (s, 5-H); mass spectrum *m/e* 440, 250. With triethylammonium formate the 6α-formyloxy compound **2c** was obtained: ir (μ) 2.9, 5.63, 5.72, 5.92; nmr (δ, $CDCl_3$) 4.37 (s, 3-H), 5.55 (s, 5-H); mass spectrum *m/e* 468, 250. Compounds **2a** and **2c** are assigned the 6α configuration by analogy with **2b**.

Low yields of **2a**, and sometimes **2c**, were always obtained, no matter which reagent was added to **6**; evidently the reactivity of **6** toward water is exceptionally great. Presumably **2c** arises from decomposition of *tert*-butyl hypochlorite to acetone, which undergoes the haloform reaction to give formate ion or its equivalent. A major by-product always formed is assigned the structure **7** on the basis of its ir, nmr, and mass spectra. Another minor by-product often seen by nmr was once isolated in low yield and identified as the 6α-benzyloxy derivative **2d**, identical with an authentic sample.[7] This can only come from addition to **6** of benzyl alcohol formed by base attack on the benzyl ester.

Hydrogenolysis[8] of **2a** with an equal weight of 10% Pd/C and equimolar $NaHCO_3$ in 4:1 MeOH–H_2O for 1 hr at 40 psi afforded 6α-hydroxypenicillin G (**1a**): nmr (δ, D_2O) 1.35 (s), 1.46 (s) (*gem*-dimethyl), 3.65 (s, $C_6H_5CH_2CO$), 4.23 (s, 3-H), 4.67 (s, HDO), 5.33 (s, 5-H), 7.25 (s, C_6H_5); mass spectrum of Me ester (from CH_2N_2) *m/e* 364. In similar fashion[8] was obtained 6α-formyloxypenicillin G (**1c**): nmr (δ, D_2O) 4.11 (s, 3-H), 4.55 (s, HDO), 5.35 (s, 5-H); mass spectrum of Me ester *m/e* 392. The antimicrobial activities of **1a** and **1c** were markedly lower than that of **1b**.

Acknowledgment.—We are grateful to Dr. L. Cama for many helpful discussions during the course of this work.

(5) Unpublished results from these laboratories.

(6) With triethylamine as base, and (presumably) at ambient temperature, the sulfur atom is chlorinated and the thiazolidine ring opened: J. C. Sheehan in "Molecular Modification in Drug Design," American Chemical Society, Washington, D. C., 1964, p 22.

(7) Prepared by Mr. W. J. Leanza by the method of ref 3.

(8) These experiments were performed by Miss N. Schelechow.

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RECEIVED JANUARY 3, 1973

Improved Routes to Methyl 4-Methylimidazole-2-carboxylate and Methyl 5-Methyl-1,2,4-triazole-3-carboxylate[1]

Summary: Triethyloxonium tetrafluoroborate and methyl fluorosulfate alkylate the sulfur atom of ethyl 2-thiooxamate. The alkylation products (**2a** and **2b**) contain nucleophilic nitrogen atoms and good leaving

(1) Full experimental details will appear following these pages in the microfilm edition of this volume of the journal. Single copies may be obtained from the Business Operations Office, Books and Journals Division, American Chemical Society, 1155 Sixteenth St., N.W., Washington, D. C. 20036. Remit check or money order for $3.00 for photocopy or $2.00 for microfiche, referring to code number JOC-73-1437.