lustrative of the utility of TMP in suppressing acid-catalyzed side reactions. 2-Phenyl-5,5-dimethyl-1,3-dioxane was also smoothly cleaved (entry 4).

The bis(ethylene acetal) of terephthalaldehyde with bromine and chlorine showed the same behavior to provide the halo esters in good yield (entry 5). Several methods for the preparation of these esters, which are highly sought for intermediates in polymer chemistry, have been described in patented procedures.[19] Most of them suffer from lengthy reaction conditions, high temperatures, difficult manipulations, and moderate yields only.[19] The present procedure has the advantages of both high yield and procedural simplicity.

With respect to the regioselectivity involved in the conversion 1 → 2, treatment of a mixture (3:2)[20] of *cis*- and *trans*-4-methyl-2-phenyl-1,3-dioxolane (1, R = C_6H_5; R′ = CH_3) with bromine in TMP at 0 °C afforded 1-methyl-2-bromoethyl benzoate and 2-methyl-2-bromoethyl benzoate (2 and 2a, R = C_6H_5; R′ = CH_3; X = Br) in the ratio 24:1, respectively (entry 6).[21] The same isomer distribution was found in the chlorination reaction. The bis(propylene acetal) of terephthalaldehyde with bromine and chlorine showed a similar trend (entry 7). This aspect coupled with the fact halogenative cleavage takes place without a radical source implies an ionic pathway indicated in Scheme I.[2-7,15] Halide attack on the ambident cation 4 from the least hindered side accounts for the major isomer formed. High regioselectivity observed in TMP may be due to solvation of the cation in the ion pair 4 resulting in reduced reactivity of the counterion.

In summary, TMP mediated halogenative cleavage is convenient and proceeds rapidly without added catalysts to give pure halo esters in high yields. In most cases, the reaction can be run in a homogeneous medium. Both neutral and mild reaction conditions should permit easily cleavable functional groups to remain intact. The present procedure is also significantly superior with respect to the regioselectivity than with the reported methods.[2-6]

Experimental Section

General Data. Melting points were determined with a Thomas–Hoover capillary melting point apparatus and are uncorrected. IR spectra were recorded on a Perkin–Elmer 727 infrared spectrophotometer. ^1H NMR spectra were obtained on a Jeol MH-100 nuclear magnetic resonance spectrometer. Elemental analyses were carried out by Galbraith Laboratories, Knoxville, Tenn. Trimethyl phosphate (TMP) was distilled over P_2O_5 (bp 52–54 °C (0.5 mm)) and stored in amber-colored bottles.

Starting Materials. The starting acetals were prepared by boiling a mixture of the aldehyde (0.5 mol), glycol (0.55 mol), anhydrous benzene (100 mL), and a catalytic amount of *p*-toluenesulfonic acid with the removal of water (Dean–Stark). After evaporation of the solvent, the residue was distilled under vacuum. Physical data are given in Table I.

General Procedure for the Preparation of Halohydrin Esters. The reactions were run at the temperatures indicated in Table I. To a magnetically stirred solution or suspension of the acetal (0.1 mol) in 50 mL of TMP, protected from moisture, bromine (17.6 g, 0.11 mol in 50 mL of TMP)[22] or chlorine (the gas was bubbled at 0 °C into 50 mL of TMP until 0.11 mol was absorbed) was added dropwise during 1 h. An exothermic reaction ensued in all the cases, and the temperature was not permitted to rise above 10 °C. During the addition, a gas (CH_3Br or CH_3Cl) was evolved. After being stirred for an additional period of time (Table I), about 300 mL of water was added with ice cooling. If an oil separated, it was extracted with hexane (3 × 50 mL), and the combined organic extract was washed with cold water (3 × 50 mL). After being stirred with anhydrous $MgSO_4$ in a hood to expel excess bromine or chlorine, the solvent was removed in a rotoevaporator, and the residue was distilled under vacuum.

If a solid was formed on dilution with water, it was filtered, washed with cold water, and recrystallized from an appropriate solvent.

Physical data and yields are given in Table I.

Bromination of 2-Cyclohexyl-1,3-dioxolane in CCl_4. To a stirred solution of the acetal (15.62 g, 0.1 mol) in 50 mL of CCl_4 cooled to 0 °C was added bromine (17.6 g, 0.11 mol) dissolved in 50 mL of CCl_4 during 1 h ($CaCl_2$ tube). The temperature of the reaction was not allowed to rise above 8 °C by controlled addition. After the solution was stirred at room temperature for 3 h, the usual workup afforded a colorless oil (24.0 g). ^1H NMR analysis of the reaction product showed it to be a mixture of 2 (R = C_6H_{11}; R′ = H; X = Br), 5, and 6. Only bromoester 2 was obtained when the above reaction was run in TMP.

Registry No. 2 (R = C_6H_5, R^1 = H, X = Br), 939-54-8; 2 (R = *p*-$CH_3C_6H_4$, R^1 = H, X = Br), 7143-95-5; 2 (R = C_6H_{11}, R^1 = H, X = Br), 36262-27-8; 2 (R = $Br(CH_2)_2$-O-CO-*p*-C_6H_4, R^1 = H, X = Br), 32676-75-8; 2 (R = $Cl(CH_2)_2$-O-CO-*p*-C_6H_4, R^1 = H, X = Cl), 1026-93-3; 2 (R = C_6H_5, R^1 = CH_3, X = Br), 6065-70-9; 2 (R = C_6H_5, R^1 = CH_3, X = Cl), 36220-92-5; 2 (R = $BrCH_2CH(CH_3)$-O-CO-*p*-C_6H_4, R^1 = CH_3, X = Br), 70659-69-7; 2 (R = $ClCH_2CH(CH_3)$-O-CO-*p*-C_6H_4, R^1 = CH_3, X = Cl), 70659-70-0; 5, 70659-71-1; 6, 70659-72-2; 2-phenyl-1,3-dioxolane, 936-51-6; 2-*p*-tolyl-1,3-dioxolane, 2403-51-2; 2-cyclohexyl-1,3-dioxolane, 4362-48-5; 5,5-dimethyl-2-phenyl-1,3-dioxane, 776-88-5; 2,2′-(1,4-phenylene)bis[1,3-dioxolane], 5660-56-0; *cis*-4-methyl-2-phenyl-1,3-dioxolane, 5932-73-0; *trans*-4-methyl-2-phenyl-1,3-dioxolane, 51591-49-2; 2,2′-(1,4-phenylene)bis[4-methyl-1,3-dioxolane], 70659-73-3; 3-bromo-2,2-dimethylpropyl benzoate, 70659-74-4; benzaldehyde, 100-52-7; *p*-methylbenzaldehyde, 104-87-0; cyclohexanecarboxaldehyde, 2043-61-0; terephthalaldehyde, 623-27-8; ethylene glycol, 107-21-1; 2,2-dimethylpropylene glycol, 126-30-7; 1,2-propylene glycol, 57-55-6.

(19) (a) Netherlands Patent 108 150 [*Chem. Abstr.*, **62**, 7696f (1965)]; (b) Japanese Patent 7503 295 [*Chem. Abstr.*, **83**, 27603z (1975)]; (c) U.S. Patent 3 280 173 [*Chem. Abstr.*, **66**, P 10767h (1967)].

(20) T. D. Inch and N. Williams, *J. Chem. Soc. C*, 263 (1970).

(21) ^1H NMR analysis was performed on the crude reaction product. At room temperature, the ratio of 2:2a is 18:1.

(22) Bromine or chlorine do not react with TMP in the dark. See ref 17.

2β-(Hydroxymethyl)penicillin

Douglas O. Spry

The Lilly Research Laboratories, Eli Lilly and Company, Indianapolis, Indiana 46206

Received March 2, 1979

Recent interest in 2β-(hydroxymethyl)penicillins as possible precursors in the biosynthetic conversion of penicillins to cephalosporins[1] prompts us to report a successful synthesis of the title compound.

The first attempt to implicate the 2-(hydroxymethyl)penicillin as a possible intermediate in the biosynthesis of penicillin and cephalosporin antibiotics was reported in 1972 by Cooper.[2] He obtained the 2β-(hydroxymethyl)penicillin 1β-oxide 1 and the corresponding lactone 2 by the oxidation of the thiazolidine azetidinone 3 (Scheme I).

Thus the corresponding 2-(hydroxymethyl)penicillin sulfides were not isolated and the yield of 1 and 2 was less than 5%.[3]

Morin et al.[4] first reported the derivatization of the β-methyl group in penicillin by obtaining 2β-(acetoxymethyl)penicillins from the Pummerer rearrangement on the penicillin sulfoxide with acetic anhydride. Since then

(1) J. E. Baldwin, S. R. Herchen, J. C. Clardy, K. Hirotsu, and T. S. Chou, *J. Org. Chem.*, **43**, 1342 (1978).

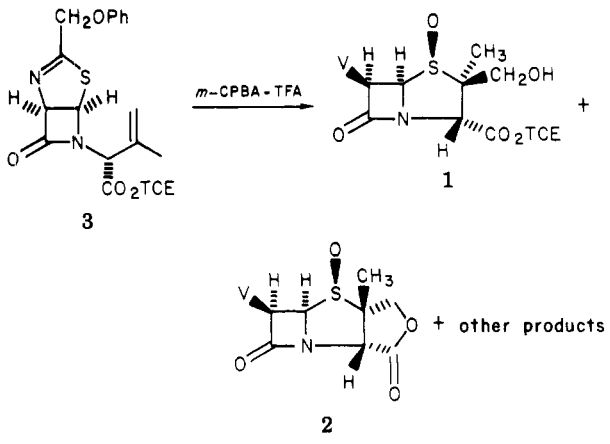
(2) R. D. G. Cooper, *J. Am. Chem. Soc.*, **94**, 1018 (1972).

(3) Personal communication with R. D. G. Cooper.

(4) R. B. Morin, B. G. Jackson, R. A. Mueller, E. R. Lavagnino, W. B. Scanlon, and S. L. Andrews, *J. Am. Chem. Soc.*, **91**, 1401 (1969).

0022-3263/79/1944-3084$01.00/0

Scheme I



3 1 2

TCE = CH_2CCl_3
V = $PhOCH_2C(O)NH$-

many other 2β-methylenepenam derivatives have been reported including halo,[5-11] alkoxy,[9] azido,[9] sulfides,[9] substituted amino,[9] and nitroxy.[6] The 2α-methylenepenam derivatives include acetoxy,[6,12,13] halo,[6,8] and nitroxy.[6]

It seemed to us, however, that utilization of any of the above derivatives to prepare (hydroxymethyl)penicillins by displacement would result in ring expansion to the cepham system or steric problems due to the neopentyl type system of the substituted penicillins. We were thus led to consider an intramolecular type cleavage of an appropriately substituted penicillin to afford the hydroxymethyl group.

Treatment of Kamiya's[7] disulfide **4** with chloroacetic acid and silver acetate gave, after careful chromatography, 35–40% of the 2β-(chloroacetoxymethyl)penicillin **5** along with ca. 8% cephem **6** and ca. 30% 3-(chloroacetoxy)-cepham **7**. Reaction of the disulfide **4** with dichloroacetic acid under the same conditions gave very little penicillin but mainly 3-substituted cepham, while trichloroacetic acid gave no penicillin and only cepham. These results indicate the propensity of the corresponding substituted penicillins, under the reaction conditions, to rearrange to the cepham system via an episulfonium ion.

Chloroacetylamines[14,15] and chloroacetates[16] are known to react with thiourea to give *S*-substituted thioamidines, which then undergo intramolecular amidinolysis to give the corresponding amine or alcohol and pseudothiohydantoin. We anticipated that the chloroacetate group of **5** would react similarly with thiourea to give the corresponding hydroxy derivative. Treatment of the 2β-(chloroacetoxymethyl)penicillin **5** with 5 mol equiv of thiourea in ethanol at 60 °C for 30 min gave a 74–84% yield of crude 2β-(hydroxymethyl)penicillin **8**. Structure of the product, (hydroxymethyl)penicillin **8**, was evident from physical data. The NMR spectrum showed loss of the chloromethylene protons at δ 4.09 and the presence of a new AB pattern for the hydroxymethyl protons at δ 3.48 and 3.76 (J = 10 Hz). The IR spectrum showed the presence of hydroxyl and the β-lactam. Mass spectrum showed a molecular ion at m/e 501 with a strong peak at m/e 483 (M − 18). Oxidation of **8** with 1 equiv of *m*-CPBA gave a high yield of the 2β-(hydroxymethyl)penicillin 1β-oxide **9**, which proved identical (TLC and NMR) with material obtained from the thiourea cleavage (65–75%) of the 2β-(chloroacetoxymethyl)penicillin 1β-oxide **10** (Scheme II).

Although **9** could be purified by silica gel chromatography and subsequent crystallization, the corresponding sulfide **8** proved unstable to silica gel chromatography, giving the lactone **11**. A similar reaction with a 3β-hydroxycepham on silica gel chromatography has been observed by Gutowski et al.[17] and indeed, when **7** was treated with thiourea followed by silica gel chromatography, the lactone **12** was isolated. The difference in stability of **8** and **9** clearly indicates the stabilizing effect of hydrogen bonding between the hydroxyl group and the sulfoxide function in compound **9** (Scheme III).

Oxidation of the sulfide of **5** with ozone[18] gave a low yield of the α-sulfoxide **13** which was thermally epimerized[12] to the α-(chloroacetoxymethylene)penicillin 1β-oxide **14**. However, because of the low yield of **13** it was not feasible to cleave **14** with thiourea to give the corresponding α-(hydroxymethyl)penicillin (Scheme IV).

Removal of the *p*-nitrobenzyl ester function from **8** and **9** by hydrogenolysis gave the corresponding acids **15** and **16** which were biologically less active than the parent penicillin.

Experimental Section

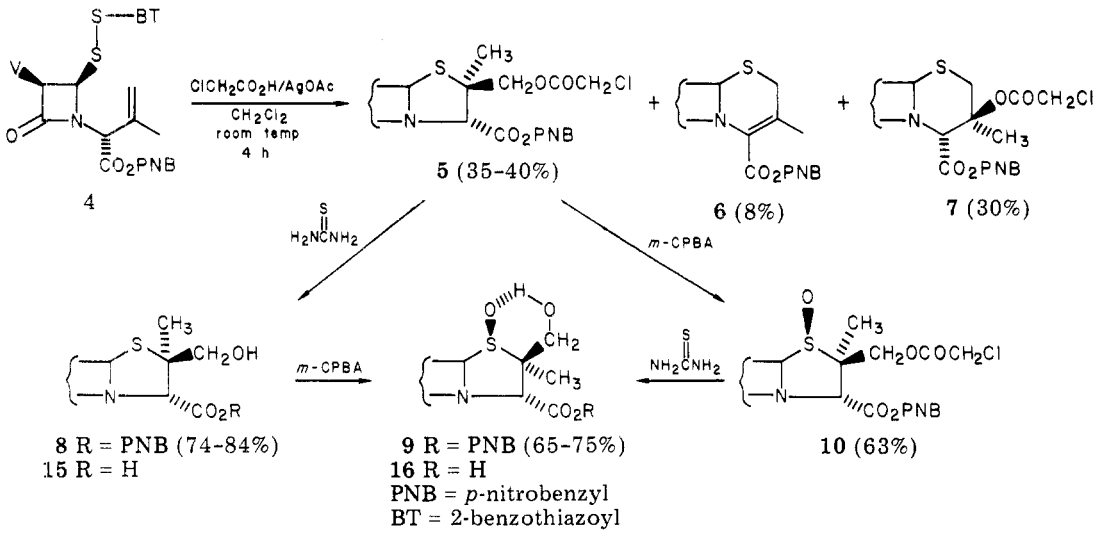
***p*-Nitrobenzyl 2β-(Chloroacetoxymethyl)-6-(phenoxyacetamido)penicillinate (5).** A mixture of 0.651 g (1.0 equiv) of the disulfide **4**, 0.340 g of AgOAc (2.08 equiv), and 4.1 g of $ClCH_2CO_2H$ (43.5 equiv) in 15 mL of CH_2Cl_2 was allowed to stir at room temperature for 4 h. The reaction mixture was filtered and the filtrate was washed with aqueous $NaHCO_3$ and brine, dried ($NaSO_4$), and chromatographed on silica gel using a toluene–ethyl acetate gradient to give 0.037 g of **6**, 0.20 g of **5**, and 0.17 g of **7**. **5**: NMR ($CDCl_3$) δ 1.46 (s, 3, α-Me), 3.95, 4.40 (AB, J = 13 Hz, 2, $CH_2OC(O)CH_2Cl$), 4.09 (s, 2, CH_2Cl), 4.56 (s, 2, $PhOCH_2$) 4.82 (s, 1, H_3), 5.28 (s, 2, PNB), 5.60 (d, J = 4 Hz, 1, H_5), 5.68 (q, J = 4, 10 Hz, 1, H_6); IR ($CHCl_3$) 1790 cm^{-1} (β-lactam).

***p*-Nitrobenzyl 2β-(Chloroacetoxymethyl)-6-(phenoxyacetamido)penicillin 1β-Oxide (10).** Oxidation of **5** was done in CH_2Cl_2 at 5 °C by dropwise addition of 1.05 equiv of *m*-chloroperbenzoic acid. After 30 min the solution was washed with $NaHCO_3$, H_2O, and brine, dried, (Na_2SO_4) and chromatographed on silica gel using toluene–ethyl acetate gradient to give 63% 1β-oxide **10**: NMR ($CDCl_3$) δ 1.22 (s, 3, α-Me), 4.15 (s, 2, CH_2Cl), 4.40, 4.83 (AB, J = 14 Hz, 2, $CH_2OC(O)CH_2Cl$), 4.55 (s, 2, $PhOCH_2$), 4.83 (s, 1, H_3), 5.13 (d, J = 4 Hz, 1, H_5), 5.35 (s, 2, PNB), 6.20 (q, J = 4, 10 Hz, 1, H_6); IR ($CHCl_3$) 1795 cm^{-1} (β-lactam).

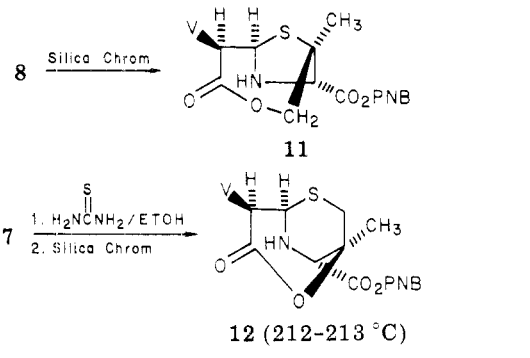
***p*-Nitrobenzyl 2β-(Chloroacetoxymethyl)-6-(phenoxyacetamido)penicillin 1α-Oxide (13).** A solution of the sulfide **5** (0.461 g) in 30 mL of acetone/12 mL of water was ozonized with excess ozone (1.59 mm/min) at −3 °C for 15 min. The solution was evaporated to dryness, taken up in CH_2Cl_2, and dried with Na_2SO_4 and then chromatographed on silica gel using a toluene–ethyl acetate gradient to give the 1α-oxide **13** in 12% yield as a froth: NMR ($CDCl_3$) δ 1.31 (s, α-Me), 4.18 (s, CH_2Cl), 4.59 (s, $PhOCH_2$), 4.85 (s, H_3), 5.39 (br, PNB, H_5, H_6); IR ($CHCl_3$) 1780 cm^{-1} (β-lactam).

(5) S. Kukolja and S. R. Lammert, *J. Am. Chem. Soc.*, **94**, 7169 (1972).
(6) S. Kukolja, S. R. Lammert, M. R. Gleissner, and A. I. Ellis, *J. Am. Chem. Soc.*, **97**, 3192 (1975).
(7) T. Kamiya, T. Teraji, Y. Saito, M. Hashimoto, O. Nakaguchi, and T. Oku, *Tetrahedron Lett.*, 3001 (1973).
(8) H. Tanida, T. Tsuji, T. Tsushima, H. Ishitobi, T. Irie, T. Yano, H. Matsumura, and K. Tori, *Tetrahedron Lett.*, 3303 (1975).
(9) T. Kamiya, T. Teraji, M. Hashimoto, O. Nakaguti, and T. Oku, U. S. Patent 3 954 732 (1976).
(10) T. Kamiya, Y. Saito, T. Teraji, O. Nakaguti, T. Oku, H. Nakamora, and M. Hashimoto, U. S. Patent, 4 009 159 (1977).
(11) S. J. Eagle and J. Kitchin, *Tetrahedron Lett.*, 4703 (1978).
(12) D. O. Spry, *J. Am. Chem. Soc.*, **92**, 5006 (1970).
(13) D. O. Spry, *J. Chem. Soc., Chem. Commun.*, 259 (1973).
(14) J. D. Cocker, B. R. Cowley, J. S. G. Cox, S. Eardley, G. I. Gregory, J. K. Lazenby, A. G. Long, J. C. P. Sly, and G. A. Sommerfield, *J. Chem. Soc.*, 5015 (1965).
(15) M. Masaki, T. Kitahara, H. Kurita, and M. Ohta, *J. Am. Chem. Soc.*, **90**, 4508 (1968).
(16) A. F. Cook and D. T. Maichuk, *J. Org. Chem.*, **35**, 1940 (1970).
(17) G. E. Gutowski, C. M. Daniels, and R. D. G. Cooper, *Tetrahedron Lett.*, 3429 (1971).
(18) D. O. Spry, *J. Org. Chem.*, **37**, 793 (1972).

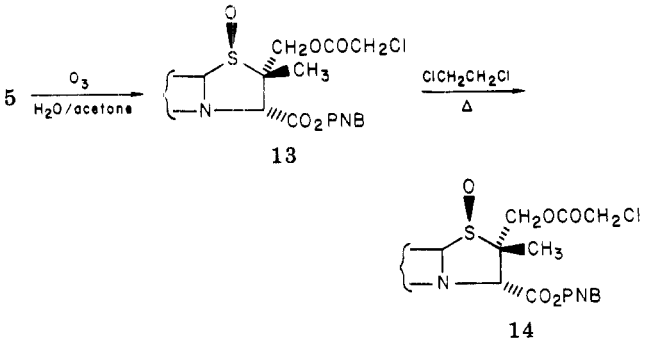
Scheme II



Scheme III



Scheme IV



***p*-Nitrobenzyl 2α-(Chloroacetoxymethyl)-6-(phenoxyacetamido)penicillin 1β-Oxide (14).** Thermal inversion of **13** in refluxing dichloroethane for 1 h gave **14**: NMR ($CDCl_3$) δ 1.76 (s, β-Me), 4.18 (s, CH_2Cl), 4.56 (s, $PhOCH_2$), 4.84 (s, H_3), 5.32 (br, PNB, H_5), 6.15 (q, J = 4, 10 Hz, H_6); IR ($CHCl_3$) 1790 cm^{-1} (β-lactam).

***p*-Nitrobenzyl 2β-(Hydroxymethyl)-6-(phenoxyacetamido)penicillinate (8).** The chloroacetoxymethyl sulfide **5** (1.55 g, 1.0 equiv) and 1.02 g (5.0 equiv) of thiourea in 60 mL of EtOH were heated at 60 °C for 30 min. The mixture was then evaporated to dryness, taken up in EtOAc–H_2O, washed with H_2O and brine, dried (Na_2SO_4), and evaporated to 1.11 g of (hydroxymethyl)-penicillin as a froth: NMR ($CDCl_3$) δ 1.38 (s, 3, α-Me), 3.48, 3.76 (AB, J = 10 Hz, 2, CH_2OH), 4.52 (s, 2, $PhOCH_2$), 4.88 (s, 1, H_3), 5.30 (s, 2, PNB), 5.6 (m, 2, H_5, H_6); IR ($CHCl_3$) 1780 cm^{-1} (β-lactam); mass spectrum m/e 501, 483 (M – 18).

***p*-Nitrobenzyl 2β-(Hydroxymethyl)-6-(phenoxyacetamido)penicillin 1β-Oxide (9).** The chloroacetoxymethyl oxide **13** (2.192 g, 1.0 equiv) and 2 equiv (0.560 g) of thiourea were heated at 60 °C for 1 h in 100 mL of EtOH. The mixture was worked up as above in **8** followed by silica gel chromatography using a toluene–ethyl acetate gradient to give 1.405 g of **9** as a white froth. Crystallization from CH_2Cl_2–hexane gave white needles: mp 155–156 °C; NMR ($CDCl_3$) δ 1.16 (s, 3, α-Me), 3.3 (br, 1, OH), 4.13 (s, 2, CH_2OH), 4.50 (s, 2, $PhOCH_2$), 4.95 (s, 1, H_3), 5.02 (d, J = 4 Hz, 1, H_5), 5.30 (s, 2, PNB), 6.10 (q, J = 4, 10 Hz, 1, H_6); IR ($CHCl_3$) 1795 cm^{-1} (β-lactam); mass spectrum m/e 483 (M – 18). Anal. Calcd for $C_{23}H_{23}N_3O_9S$: C, 53.38; H, 4.48; N, 8.12. Found: C, 53.65; H, 4.28; N, 7.97.

***p*-Nitrobenzyl 5-(phenoxyacetamido)-3-oxa-9-thia-7-azabicyclo[4.2.1]nonane-8-carboxylate (11)** was obtained as a white froth from silica gel chromatography of **8**: NMR ($CDCl_3$) δ 1.33 (s, 3, Me), 3.8 (br, 1, NH), 4.20 (s, 1, H_3), 4.23, 4.45 (AB, J = 12 Hz, 2, CH_2O), 4.55 (s, 2, $PhOCH_2$), 5.18 (m, 2, H_5, H_6), 5.32 (s, 2, PNB); IR ($CHCl_3$) 1730 cm^{-1}; mass spectrum m/e 501.

2β-(Hydroxymethyl)-6-(phenoxyacetamido)penicillin 1β-oxide (16): NMR ($CDCl_3$) δ 1.36 (s, 3, α-Me), 4.20 (s, 2, CH_2OH), 4.56 (s, 2, $PhOCH_2$), 4.73 (s, 1, H_3), 5.02 (d, J = 4 Hz, 1, H_5), 6.05 (q, J = 4, 10 Hz, 1, H_6); IR ($CHCl_3$) 1795 cm^{-1} (β-lactam).

2β-(Hydroxymethyl)-6-(phenoxyacetamido)penicillin (15): NMR ($CDCl_3$) δ 1.53 (s, 3, α-Me), 3.50, 3.69 (AB, J = 12 Hz, 2, CH_2OH), 4.60 (s, 2, $PhOCH_2$), 4.75 (s, 1, H_3), 5.7 (m, 2, H_5, H_6); IR ($CHCl_3$) 1775 cm^{-1} (β-lactam).

Registry No. **4**, 70850-41-8; **5**, 70850-42-9; **6**, 28974-31-4; **7**, 70850-43-0; **8**, 70850-44-1; **9**, 70850-45-2; **10**, 70850-46-3; **11**, 70850-47-4; **13**, 70878-66-9; **14**, 70850-48-5; **15**, 70850-49-6; **16**, 70850-50-9.

Synthesis of Some Non-K-Region Derivatives of Dibenz[*a*,*h*]anthracene

Nitya G. Kundu

School of Pharmacy LAC/USC Cancer Research Laboratory, University of Southern California, Los Angeles, California 90033

Received January 3, 1979

Since polycyclic hydrocarbons have been shown to have carcinogenic activity,[1-5] considerable progress has been made to elucidate the molecular mechanism of chemical carcinogenesis due to these hydrocarbons and related

(1) E. L. Keenaway and I. Hieger, *Brit. Med. J.*, 1, 1044 (1930).
(2) J. W. Cook, I. Hieger, E. L. Keenaway, and W. V. Mayneord, *Proc. R. Soc. London, Ser. B*, 3, 456 (1932).
(3) H. Burrows, I. Hieger, and E. L. Keenaway, *Am. J. Cancer*, 16, 57 (1932).
(4) H. Burrows, *Proc. R. Soc. London, Ser. B*, 3, 238 (1932).
(5) G. Barry and J. W. Cook, *Am. J. Cancer*, 20, 58 (1934).

0022-3263/79/1944-3086$01.00/0