To this solution, 0.5 mmol of a Cyt derivative, **8a**, **8c**, **18b**, **18c**, or 5-bromo-1,3-dimethylcytosine (**38**), in 0.3 mL of MeOH was added. This admixture was stirred for a period of time (see Table II) and then evaporated until dry under reduced pressure at 22 °C. The residue was dissolved in acetone, and the product was precipitated by the dropwise addition of ethyl acetate. The precipitate was collected and redissolved in acetone. Ethyl acetate was again added to the solution just prior to it becoming permanently cloudly. This clear solution was refrigerated, and the crystalline product was collected. Reaction conditions, results, and product properties are given in Table II.

**Preparation of 5-Bromo-6-hydroxy-5-methyl-5,6-dihydrocytosine (27) and 5-Bromo-6-hydroxy-$N^4$,5-dimethyl-5,6-dihydrocytosine (28).** 5-Methylcytosine (**39**, 1 mmol) in 3 mL of water was treated with 1.1 mmol of NBS. The mixture was stirred for 3 h and then refrigerated overnight. The crystalline product was collected. $N^4$,5-Dimethylcytosine (**40**) was treated in a similar manner. However, 1 mL of water was used as solvent, and the reaction time required was ~1 h. After lyophilization, the residue was triturated with $CHCl_3$ and the product isolated. Further information regarding the reactions and the products is presented in Table II.

**Preparation of 5,5-Dibromo-6-hydroxy-5,6-dihydrocytidine (9b), 5-Bromo-6-hydroxy-1,$N^4$-dimethyl-5,6-dihydrocytosine (20), 5,5-Dibromo-6-hydroxy-1,$N^4$-dimethyl-5,6-dihydrocytosine (21), and 5-Bromo-6-hydroxy-1,$N^4$,$N^4$-trimethyl-5,6-dihydrocytosine (29).** One millimole of 5-bromocytidine (**8b**), 1,$N^4$-dimethylcytosine (**18b**), 5-bromo-1,$N^4$-dimethylcytosine (**18c**), and 1,$N^4$,$N^4$-trimethylcytosine (**41**) in 10, 2, 1, and 0.3 mL of water, respectively, was treated with 1.1 mmol of NBS. The solution was stirred at room temperature for a period of time and then refrigerated overnight. The crystalline product was collected. [See Table II for additional infomation.]

**Acknowledgment.** The authors wish to thank the early successful study made by M. Apicella and M. Mouyos. The NMR spectra were taken at the Middle Atlantic NMR Facility at the University of Pennsylvania in Philadelphia, under the supervision of Dr. George McDonald. This work was supported by a grant from the National Institutes of Health (Grant No. 5 R01 GM24238).

**Registry No. 3a**, 51-20-7; **4a**, 1124-83-0; **6a**, 71-30-7; **6b**, 65-46-3; **8a**, 2240-25-7; **8a**·HBr, 71647-17-1; **8b**, 3066-86-2; **8c**, 65567-60-4; **9b**, 71647-18-2; **18a**, 1122-47-0; **18b**, 6220-49-1; **18c**, 71647-19-3; **18c**·HBr, 71647-20-6; **20**, 71647-21-7; **21**, 71647-22-8; **22**, 71647-23-9; **23**, 71647-24-0; **24**, 71647-25-1; **25**, 71647-26-2; **26**, 71647-27-3; **27**, 71647-28-4; **28**, 71647-29-5; **29**, 71647-30-8; **38**, 64236-15-3; **39**, 554-01-8; **40**, 62006-34-2; **41**, 2228-27-5; bromine, 7726-95-6; ammonium bromide, 12124-97-9; NBS, 128-08-5.

**Supplementary Material Available:** Expanded version of Figure 5 showing additional time curves (2 pages). Ordering information is given on any current masthead page.

# Phosphinimines as Useful Intermediates in the Synthesis of 3-(Acylamino)-β-lactams

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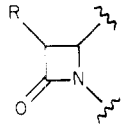
*Received June 21, 1979*

N-Substituted 3-azido-4-(methylthio)-2-azetidinones **9** (trans) and **10** (cis) reacted with triphenylphosphine to give the corresponding 3-phosphinimino-β-lactams **11** and **12**. Treatment of these iminophosphoranes with phenoxyacetyl chloride afforded respectively the *trans*- and *cis*-3-(acylamino)-β-lactams **13** and **14**. The *cis*-β-lactam **14** was obtained also from the *trans*-β-lactam **11**: condensation of **11** with *p*-nitrobenzaldehyde gave the Schiff base **19**; kinetically controlled epimerization of **19**, followed by hydrolysis and acylation, afforded the β-lactam **14**.

The azido group has been used as a progenitor of the acylamino side chain in some total syntheses of penicillins,[1] cephalosporins,[1] and various analogues of these β-lactam antibiotics.[2-12] In these papers, 3-azidoazetidinones, represented by the partial structure **1**, were reduced by catalytic hydrogenation, hydrogen sulfide in the presence of ammonia or triethylamine, or zinc in acetic acid to the corresponding 3-aminoazetidinones **2**. Compounds **2** were subsequently converted into 3-(acylamino)azetidinones **3**.



**1**, R = $N_3$
**2**, R = $NH_2$
**3**, R = R′CONH
**4**, R = $Ph_3P{=}N$
**5**, R = *p*-$O_2NC_6H_4CH{=}N$

(1) R. A. Firestone, N. S. Maciejewicz, R. W. Ratcliffe, and B. G. Christensen, *J. Org. Chem.*, **39**, 437 (1974), and references cited therein.
(2) A. K. Bose, G. Spiegelmen, and M. S. Manhas, *J. Am. Chem. Soc.*, **90**, 4506 (1968).
(3) L. D. Cama and B. G. Christensen, *J. Am. Chem. Soc.*, **96**, 7582 (1974); *Tetrahedron Lett.*, 4233 (1978).
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(5) J. A. Edwards, A. Guzman, R. Johnson, P. J. Beeby, and H. H. Fried, *Tetrahedron Lett.*, 2031 (1974).
(6) A. K. Bose, G. Spiegelman, and M. S. Manhas, *J. Chem. Soc. C*, 2468 (1971).
(7) M. D. Bachi and O. Goldberg, *J. Chem. Soc., Perkin Trans. 1*, 2332 (1972).
(8) R. Lattrel and G. Lohaus, *Justus Liebigs Ann. Chem.*, 901 (1974).
(9) M. D. Bachi, N. Frydman, S. Sasson, C. Stern, and J. Vaya, *Tetrahedron Lett.*, 641 (1977).
(10) W. F. Huffman, K. G. Holden, T. F. Buckley III, J. G. Gleason, and L. Wu, *J. Am. Chem. Soc.*, **99**, 2353 (1977), and subsequent paper in the same series.
(11) T. T. Conway, G. Lim, J. L. Douglas, M. Menard, T. W. Doyle, P. Rivest, D. Horning, L. R. Morris, and D. Cimon, *Can. J. Chem.*, **56**, 1335 (1978), and previous papers in the same series.
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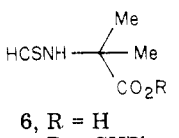
0022-3263/79/1944-4393$01.00/0 

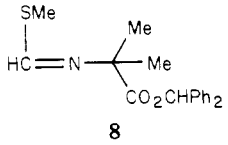
Despite the successful use of this simple reaction sequence, it cannot be considered of general applicability. In fact, in at least one case a different reaction pattern has been reported.[13] More difficulties are to be expected on extending this procedure to the synthesis of β-lactams which exhibit a particularly high chemical activity toward nucleophilic agents. The ability of β-lactams to acylate nucleophiles has been correlated to their antibacterial activity and has been taken into consideration in the design of new antibiotics.[14] It was therefore felt that a method for the conversion of 3-azidoazetidinones **1** into 3-(acylamino)azetidinones **3** which avoids the intermediacy of compounds having a free amino group may, in certain cases, be advantageous. A synthetic route of this kind, which is based on the intermediacy of phosphinimines of type **4**, is described in the present paper. Compounds **4** also proved to be useful synthetic precursors of Schiff bases **5** which were employed for the "correction" of the stereochemistry of the β-lactam ring according to the Merck procedure.[1]

The substrates for the present investigation were nonfused β-lactams which, like the natural penicillins and cephalosporins, bear a carboxylic (or an ester) group on the carbon atom attached to the ring nitrogen atom, a nitrogen substituent at the 3-position, and a sulfur substituent at the 4-position. This type of compound can be obtained by building the azetidinone on the nitrogen atom of α-aminocarboxylic acids.[15] To avoid the introduction of an additional chiral center, we chose α-aminoisobutyric acid as a model.

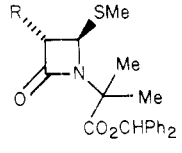
Condensation of α-aminoisobutyric acid with *O*-ethyl thionoformate gave the thioformamide **6** (42%). Esterification of **6** with diphenyldiazomethane afforded **7** (68%) which was S-methylated with methyl iodide and potassium carbonate to give the thioformimidate **8** (96%). Reaction



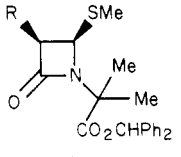
6, R = H
7, R = $CHPh_2$



8



9, R = $N_3$
11, R = $Ph_3P{=}N$
13, R = $PhOCH_2CONH$



10, R = $N_3$
12, R = $Ph_3P{=}N$
14, R = $PhOCH_2CONH$

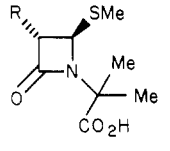
of **8** with azidoacetyl chloride in the presence of triethylamine afforded, after chromatography, the *trans*-β-lactam **9** (83%) and the *cis*-β-lactam **10** (6%). The reaction between 2-heterosubstituted acetic acid chlorides, including azidoacetyl chloride, and *S*-alkylthioformimidates has been known to give exclusively *trans*-β-lactams;[7,9,15] the formation of **10** constitutes the first case, in which a *cis*-β-lactam was obtained directly from a thioformimidate. The azides **9** and **10** were converted into the corresponding iminophosphoranes **11** and **12** with triphenylphosphine. Treatment of **11** with phenoxyacetyl chloride followed by aqueous workup gave the *trans*-(acylamino)-β-lactam **13** in 75% yield based on **9**. The cis isomer **12** was similarly converted into **14** (62%).

This method was found to be effective also with compounds bearing a free carboxylic group in place of the ester grouping. Thus, treatment of **9** with trifluoroacetic acid and anisole afforded the acid **15** (89%). Addition of triphenylphosphine to **15** in chloroform afforded the phosphinimine **16** which was treated with phenoxyacetyl chloride and triethylamine to give, after workup with aqueous potassium bicarbonate, the (acylamino)-β-lactam **17** (44%). Esterification of **17** with diphenyldiazomethane gave **13** which was identical with the compound obtained as previously described in the sequence **9** → **11** → **13**. The acid **16** was obtained also on treatment of **11** with trifluoroacetic acid.

The reaction of triphenylphosphine and alkyl azides which results in the formation of *N*-alkylphosphinimines is well documented.[16,17] On the other hand, there are only a couple of references to the reaction of acyl halides with *N*-alkyl tertiary phosphinimines. In these papers imidoyl halides **18** were obtained.[18,19]

It is possible that the transformations of **11** to **13** and **12** to **14** involved the intermediacy of imidoyl chloride derivatives of type **18** which were hydrolyzed during the workup to the respective amides **13** and **14**. A very low-yield conversion of a 7-azido-7-methoxycephem into a 7-methoxycephalosporin system, involving the intermediacy of a phosphinimine, has recently been reported.[20]

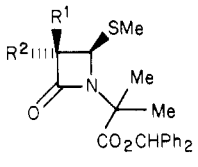
A major drawback in the synthesis of β-lactam antibiotics, or their nuclear analogues, by the method based on the cycloaddition of azidoacetyl chloride to the C=N bond of a thiazoline,[1,2,12] thiazine,[1] or other thioformimidates[7,8] lay in the resulting trans stereochemistry of the nitrogen and sulfur substituents. To obtain the cis stereochemistry as found in the natural products, the Merck group developed a method for the kinetically controlled isomerization of 6α-aminopenicillins and 7α-aminocephalosporins to their β-epimers.[1] This procedure, which has so far been applied to bicyclic systems, proves now to be effective also with nonfused β-lactams. Thus, the reaction between the phosphinimine **11** and *p*-nitrobenzaldehyde afforded the Schiff base **19** (87%) and triphenylphosphine oxide.



15, R = $N_3$
16, R = $Ph_3P{=}N$
17, R = $PhOCH_2CONH$



18



19, $R^1$ = H; $R^2$ = *p*-$NO_2C_6H_4CH{=}N$
20, $R^1$ = Li; $R^2$ = *p*-$NO_2C_6H_4CH{=}N$
21, $R^1$ = *p*-$NO_2C_6H_4CH{=}N$; $R^2$ = H
22, $R^1$ = H; $R^2$ = $NH_2$
23, $R^1$ = $NH_2$; $R^2$ = H

(13) M. S. Manhas, J. S. Chib, and A. K. Bose, *J. Org. Chem.*, **38**, 1238 (1973).
(14) See, for example, the synthesis of penems: I. Ernest, J. Gosteli, C. W. Greengrass, W. Holick, D. E. Jackman, H. R. Pfaendler, and R. B. Woodward, *J. Am. Chem. Soc.*, **100**, 8214 (1978).
(15) M. D. Bachi and K. J. Ross-Petersen, *J. Chem. Soc., Perkin Trans. 1*, 2525 (1975), and references cited therein.
(16) G. Singh and H. Zimmer, *Organomet. Chem. Rev.*, **2**, 279 (1967).
(17) A. W. Johnson, "Ylide Chemistry", Academic Press, New York and London, 1966, Chapter 6.
(18) E. Zbiral and E. Bauer, *Phosphorus*, **2**, 35 (1972).
(19) T. Hiraoka, K. Iino, Y. Iwano, T. Saito, and Y. Sugimura, *Chem. Soc., Spec. Publ.*, **No. 28**, 126 (1977).
(20) T. Hiraoka, Y. Sugimura, T. Saito, and T. Kobayashi, *Heterocycles*, **8**, 719 (1977).

Treatment of 19 in ether with phenyllithium gave the lithium derivative 20. Protonation of 20 under kinetically controlled conditions afforded a 1:1 mixture of the *trans*-β-lactam 19 and the *cis*-β-lactam 21. In the epimerization of benzyl 6β-(*p*-nitrobenzylideneamino)penicillanate, a 1:2 trans to cis ratio was reported.[1] The rigid five-membered ring fused to the β-lactam moiety in the penicillin system is obviously a better control element than the smaller, freely rotating, methylthio group in 20.

Treatment of the mixture of 19 and 21 with 2,4-dinitrophenylhydrazine and *p*-toluenesulfonic acid gave a mixture of the *trans*- and *cis*-aminoazetidinones 22 and 23 which were acylated with phenoxyacetyl chloride. Chromatography of the mixture gave the *trans*-(phenoxyacetamino)-azetidinone 13 (39%) and its cis isomer 14 (38%). These compounds were identical with the products of direct acylation of the respective phosphinimines 11 and 12.

## Experimental Section

**2-(Thioformylamino)isobutyric Acid (6).** To a solution of 2-aminoisobutyric acid (10.3 g, 0.1 mol) in chloroform (300 mL) which was saturated at 0 °C with hydrogen sulfide were added triethylamine (18.1 g, 0.18 mol) and ethyl thionoformate (20 mL). The mixture was kept for 16 h at room temperature and then evaporated. The residue was taken up with water (100 mL), mixed with ethyl acetate (200 mL), and acidified with 3 N hydrochloric acid to pH 3. The aqueous phase was extracted with ethyl acetate, and the combined organic fractions were washed with water, dried ($MgSO_4$), and evaporated. The residue was crystallized from ether to give the thioformamide 6 (6.1 g, 42%): mp 84–85 °C; NMR [$(CD_3)_2CO$ and $D_2O$] δ 1.62 (s) and 1.66 (s) (6 H), 9.3 (br, 1 H). Anal. Calcd for $C_5H_9NO_2S$: C, 40.81; H, 6.17. Found: C, 40.65; H, 6.26.

**Diphenylmethyl 2-(Thioformylamino)isobutyrate (7).** To a solution of the acid 6 (5.5 g, 37.4 mmol) in dry acetone (100 mL) was added a solution of diphenyldiazomethane in acetone (40 mmol). After 2 h, the mixture was evaporated, and the residue was triturated with ether and then crystallized from $CH_2Cl_2$–hexane to give the ester 7 (8.0 g, 68%): mp 112–114 °C; IR (KBr) 3300, 1720, 1540 $cm^{-1}$; NMR ($CDCl_3$) δ 1.58 (s, 6 H), 6.90 (s, 1 H), 7.30 (s, 10 H), 8.30 (br, 1 H), 9.30 (d, 1 H, $J$ = 14 Hz). Anal. Calcd for $C_{18}H_{19}NO_2S$: C, 68.99; H, 6.11; N, 4.47; S, 10.21. Found: C, 68.88; H, 6.26; N, 4.40; S, 10.28.

**Methyl *N*-[1-((Diphenylmethoxy)carbonyl)-1-methylethyl]thioformimidate (8).** To a stirred mixture of the thioformamide 7 (1 g, 3.2 mmol) and potassium carbonate (0.5 g, 3.6 mmol) in acetone (30 mL) was added methyl iodide (0.9 g, 5.76 mmol). Stirring was continued for 16 h, the salts were filtered off, and the filtrate was evaporated to give the thioformimidate 8 (1 g, 96%): IR ($CHCl_3$) 1730, 1590 $cm^{-1}$; NMR ($CDCl_3$) δ 1.43 (s, 6 H), 2.23 (s, 3 H), 6.78 (s, 1 H), 7.25 (s, 10 H), 8.1 (s, 1 H). This compound was used in the next step without further purification.

**3-Azido-1-[1-((diphenylmethoxy)carbonyl)-1-methylethyl]-4-(methylthio)-2-azetidinones 9 and 10.** To a stirred solution of the thioformimidate 8 (6.8 g, 20.7 mmol) and triethylamine (3.2 g, 32 mmol) in toluene (200 mL) was added a solution of azidoacetyl chloride (3.58 g, 30 mmol) in toluene (150 mL) under an argon atmosphere during 6 h. After an additional 12 h, another portion of triethylamine (3.2 g, 32 mmol) was added followed by a second dropwise addition (6 h) of a solution of azidoacetyl chloride (3.58 g, 30 mmol) in toluene (150 mL). After an additional 16 h, the mixture was filtered through Celite, evaporated, and chromatographed (silica gel, hexane–acetone) to give a mixture of the trans and cis isomers 9 and 10. Crystallization from ether afforded the trans isomer 9 (7.1 g, 83%): mp 80 °C; IR ($CHCl_3$) 2110, 1775, 1735 $cm^{-1}$; NMR ($CDCl_3$) δ 1.70 (s, 3 H), 1.75 (s, 3 H), 1.96 (s, 3 H), 4.52 (d, 1 H, $J$ = 2 Hz), 4.63 (d, 1 H, $J$ = 2 Hz), 7.03 (s, 1 H), 7.43 (s, 10 H); MS $m/e$ 382 ($M^+ - N_2$). Anal. Calcd for $C_{21}H_{22}N_4O_3S$: C, 61.44; H, 5.40; N, 13.65; S, 7.81. Found: C, 61.27; H, 5.55; N, 14.05; S, 8.12. Evaporation of the filtrate followed by chromatography gave the cis isomer 10 (0.5 g, 6%): oil; IR ($CHCl_3$) 2105, 1770, 1735 $cm^{-1}$; NMR ($CDCl_3$) δ 1.61 (s, 3 H), 1.72 (s, 3 H), 1.97 (s, 3 H), 4.66 (d, 1 H, $J$ = 5 Hz), 4.83 (d, 1 H, $J$ = 5 Hz), 6.86 (s, 1 H), 7.26 (s, 10 H); MS $m/e$ 382 ($M^+ - N_2$).

**Acidolysis of the Diphenylmethyl Ester 9.** To a solution of the ester 9 (200 mg, 0.49 mmol) in anisole (0.2 mL), at 0 °C under argon, was added trifluoroacetic acid (2 mL). After 5 min the trifluoroacetic acid was removed under reduced pressure, and the residue was taken up with chloroform and then extracted with 4% aqueous $KHCO_3$. The aqueous fraction was acidified with phosphoric acid to pH 2.5 and extracted with chloroform. The solution was dried ($MgSO_4$) and evaporated to give the free acid 15 (106 mg, 89%): IR ($CHCl_3$) 2110, 1765, 1715 $cm^{-1}$; NMR ($CDCl_3$) δ 1.71 (s) and 1.75 (s) (6 H), 2.20 (s, 3 H), 4.62 (d, 1 H, $J$ = 1.5 Hz), 4.81 (d, 1 H, $J$ = 1.5 Hz), 9.97 (s, 1 H).

**3-Phosphinimino-2-azetidinones 11, 12, and 16. A.** To a solution of the azido lactam 9 (200 mg, 0.49 mmol) in benzene (4 mL) was added triphenylphosphine (133 mg, 0.5 mmol). After 15 min the solution was evaporated, and the residue was crystallized from ether to give the phosphinimine 11 (300 mg, 90%): mp 132 °C; IR (KBr) 1765, 1730 $cm^{-1}$; NMR ($CDCl_3$) δ 1.58 (s, 3 H), 1.71 (s) and 1.75 (s) (6 H), 4.33 (dd, 1 H, $J$ = 1.5 and 26 Hz), 4.66 (d, 1 H, $J$ = 1.5 Hz), 7.01 (s, 1 H), 7.25–8.12 (m, 25 H). Anal. Calcd for $C_{39}H_{37}N_2O_3SP$: C, 72.68; H, 5.74; N, 4.35; S, 4.97. Found: C, 72.65; H, 5.78; N, 4.45; S, 5.13.

**B.** The azidolactam 10 was treated with triphenylphosphine as described in A for its isomer 9 to give the phosphinimine 12 (quantitative): NMR ($CDCl_3$) δ 1.67 (s, 3 H), 1.85 (s, 3 H), 2.22 (s, 3 H), 4.70 (dd, 1 H, $J$ = 4.5 and 28 Hz), 4.75 (d, 1 H, $J$ = 4.5 Hz), 7.0 (s, 1 H), 7.3–8.2 (m, 25 H).

**C.** To a solution of the azidolactam 15 (150 mg, 0.61 mmol) in chloroform (5 mL) was added triphenylphosphine (162 mg, 0.61 mmol). After 30 min the solution was evaporated and the residue washed with benzene to give the phosphinimine 16 (286 mg): oil; IR ($CHCl_3$) 1760 $cm^{-1}$ (br), no absorption band for $N_3$; NMR ($CDCl_3$) δ 1.42 (s) and 1.55 (s) (6 H), 1.83 (s, 3 H), 3.83 (dd, 1 H, $J$ = 2.0 and 14 Hz), 5.37 (d, 1 H, $J$ = 2.0 Hz), 7.19–8.16 (m, 15 H), 8.38 (br s, 1 H).

**D.** The trifluoroacetate of 16 was obtained by an alternative way. To a solution of the phosphinimine 11 (100 mg, 0.15 mmol) in anisole (0.3 mL), at 0 °C under argon, was added trifluoroacetic acid (2 mL). After 5 min the mixture was evaporated under reduced pressure, and the residue was triturated with ether to give the trifluoroacetic acid salt of 16 (76 mg, quantitative): NMR ($CDCl_3$) δ 1.55 (s) and 1.59 (s) (6 H), 1.78 (s, 3 H), 3.83 (br) and 4.03 (br) (1 H), 5.19 (br, 1 H), 7.59–8.08 (m, 15 H), 8.98 (br). Anal. Calcd for $C_{28}H_{28}N_2O_5F_3SP$: C, 56.75; H, 4.76. Found: C, 56.65; H, 4.62.

***trans*-1-[1-((Diphenylmethoxy)carbonyl)-1-methylethyl]-4-(methylthio)-3-(phenoxyacetamido)-2-azetidinone (13).** To a solution of 11 [prepared as described in the previous section from 100 mg (0.24 mmol) of 9] in $CH_2Cl_2$ (4 mL), at 0 °C, was added a solution of phenoxyacetyl chloride (39 mg, 0.23 mmol) in $CH_2Cl_2$ (0.5 mL) during 15 min. After 1 h at 0 °C and an additional 1 h at 25 °C, a solution of 4% aqueous $KHCO_3$ was added with stirring. Stirring was continued for an additional 20 min, and then the organic layer was washed with water, dried ($MgSO_4$), and evaporated. Crystallization of the residue (ether) gave the title compound 13 (95 mg, 75% from 9): mp 115–117 °C; IR (KBr) 1770, 1730, 1660 $cm^{-1}$; NMR ($CDCl_3$) δ 1.73 (s) and 1.75 (s) (6 H), 2.0 (s, 3 H), 4.51 (s, 2 H), 4.69 (d, 1 H, $J$ = 2 Hz), 4.85 (dd, 1 H, $J$ = 2 and 8 Hz), 6.88 (s) and 7.98 (s) and 6.80–7.50 (m) (16 H). Anal. Calcd for $C_{29}H_{30}N_2O_5S$: C, 67.16; H, 5.83; N, 5.40; S, 6.18. Found: C, 67.05; H, 5.90; N, 5.54; S, 6.28.

***cis*-1-[1-((Diphenylmethoxy)carbonyl)-1-methylethyl]-4-(methylthio)-3-(phenoxyacetamido)-2-azetidinone (14).** To a solution of 12 (127 mg, 0.2 mmol) in $CH_2Cl_2$ (5 mL) was added a solution of phenoxyacetyl chloride (34 mg, 0.20 mmol) in $CH_2Cl_2$ (0.5 mL) at 0 °C during 15 min. The product obtained after workup as described above for the preparation of 13 was chromatographed (silica gel, hexane–acetone) to give the title compound 14 (62 mg, 62%): oil; IR ($CHCl_3$) 1770, 1740, 1685 $cm^{-1}$; NMR ($CDCl_3$) δ 1.67 (s) and 1.73 (s) and 1.78 (s) (9 H), 4.59 (s, 2 H), 4.86 (d, 1 H, $J$ = 4.5), 5.60 (dd, 1 H, $J$ = 4.5 and 9.5 Hz), 6.83–7.50 (m) and 7.35 (s) (16 H). Anal. Calcd for $C_{29}H_{30}N_2O_5S$: C, 67.16; H, 5.83; N, 5.40; S, 6.18. Found: C, 67.15; H, 5.91; N, 5.20; S, 5.92. Compound 14 was obtained also from the *trans*-lactam 11 as described in the last section.

**1-(1-Carboxy-1-methylethyl)-3-(methylthio)-4-(phenoxyacetamido)-2-azetidinone (17).** To a solution of the phosphinimine **16** (87 mg, 0.18 mmol) and triethylamine (40 mg, 0.4 mmol) in $CH_2Cl_2$ (3 mL), at 0 °C under argon, was added a solution of phenoxyacetyl chloride (34 mg, 0.2 mmol) in $CH_2Cl_2$ (0.5 mL) during 10 min. After 2 h a cold 4% aqueous $KHCO_3$ solution was added with stirring. The organic phase was extracted with water, and the combined aqueous extracts were mixed with ether and then acidified to pH 2.5 with 10% $H_3PO_4$. The aqueous fraction was extracted with ether, and the combined etheral fractions were dried and evaporated to give the title compound **17** (28 mg, 44 %): oil; IR ($CHCl_3$) 1760, 1710, 1680 $cm^{-1}$; NMR ($CDCl_3$) $\delta$ 1.70 (s, 6 H), 2.19 (s, 3 H), 4.54 (s, 2 H), 4.90 (m, 2 H), 6.0 (br, 2 H), 6.7–7.8 (m, 5 H). Treatment of a sample of **17** in $CH_2Cl_2$ with diphenyldiazomethane in acetone gave the diphenylmethyl ester **13**, identical in its physical data with an authentic sample prepared as described in a previous section.

**Conversion of the *trans*-Azidolactam 9 to the *cis*-(Acylamino)lactam 14 through the Intermediacy of 11, 19, 20, 21, and 23.** To a solution of **11** obtained as previously described from 164 mg (0.4 mmol) of **9**, in benzene (4 mL) was added *p*-nitrobenzaldehyde (65 mg, 0.43 mmol). After 2 h the mixture was evaporated under reduced pressure, and the residue was washed with ether to give the Schiff base **19** (180 mg, 87%): oil; IR ($CHCl_3$) 1760, 1740, 1630 $cm^{-1}$; NMR ($CDCl_3$) $\delta$ 1.76 (s) and 1.80 (s) (6 H), 2.04 (s, 3 H), 4.77 (d, 1 H, $J$ = 2 Hz), 5.00 (d, 1 H, $J$ = 2 Hz), 6.93 (s, 1 H), 7.37 (br s, 10 H), 7.88 (d, 2 H, $J$ = 9 Hz), 8.25 (d, 2 H, $J$ = 9 Hz), 8.57 (s, 1 H). To the Schiff base **19** (150 mg, 0.29 mmol) in THF (4 mL), under argon at −68 °C, was added a solution of PhLi (0.29 mmol) in ether. After 5 min, DMF (5 mL) was added followed by an immediate quenching with a solution of AcOH (0.3 mL) and $H_2O$ (0.3 mL) in THF (2 mL). The reaction mixture was brought to room temperature and then diluted with benzene (20 mL) and washed with water, pH 4.4 buffered phosphate solution, pH 8 buffered phosphate solution, and again water. The NMR spectrum of the residue obtained after drying and evaporation indicated the presence of a 1:1 mixture of the Schiff bases **19** and **21**. NMR ($CDCl_3$) of **21**: $\delta$ 1.74 (s), 1.80 (s), 2.00 (s), 5.04 (formal q). The *p*-nitrobenzylidene grouping was removed from **19** and **21** with 2,4-dinitrophenylhydrazine (60 mg, 0.3 mmol) and *p*-toluenesulfonic acid (59 mg, 0.3 mmol) in ethanol (4 mL),[1] to give a mixture of the amines **22** and **23**. To a solution of the crude product and triethylamine (37 mg, 0.37 mmol) in $CH_2Cl_2$, under argon at 0 °C, was added a solution of phenoxyacetyl chloride (51 mg, 30 mmol) in $CH_2Cl_2$ (0.5 mL) during 15 min. After another 2 h the mixture was washed with 5% aqueous $H_3PO_4$, 4% aqueous $KHCO_3$, and water, dried, and evaporated. The NMR spectrum of the residue indicated the presence of a 1:1 mixture of **13** and **14**. Treatment of the product with ether resulted in the crystallization of **13** (48 mg). The mother liquor was evaporated, and the residue was chromatographed on a silica gel plate (hexane–acetone) to give **14** (56 mg, 38% yield based on **21**) and a second portion (12 mg) of **13**. The spectral data of these samples of **13** and **14** were identical with those of the fully characterized compounds described in previous sections.

**Registry No.** **6**, 71537-37-6; **7**, 71537-38-7; **8**, 71537-39-8; **9**, 71537-40-1; **10**, 71537-41-2; **11**, 71537-42-3; **12**, 71537-43-4; **13**, 71537-44-5; **14**, 71537-45-6; **15**, 71537-46-7; **16**, 71565-59-8; **16** trifluoroacetate salt, 71565-60-1; **17**, 71537-47-8; **19**, 71537-48-9; **21**, 71537-49-0; **22**, 71537-50-3; **23**, 71537-51-4; 2-aminoisobutyric acid, 62-57-7; ethyl thionoformate, 29392-46-9; diphenyldiazomethane, 883-40-9; azidoacetyl chloride, 30426-58-5; trifluoroacetic acid, 354-32-5; triphenylphosphine, 603-35-0; phenoxyacetyl chloride, 701-99-5; *p*-nitrobenzaldehyde, 555-16-8.

# Diels–Alder Cycloaddition of Juglone Derivatives. 2. Regiospecificity of Reactions Leading to Tetracyclic Anthracyclinone Systems[1]

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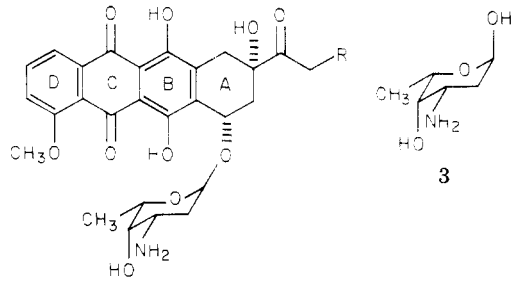
*Received May 30, 1979*

The regiospecificity of the reaction of several juglone derivatives with two complex dienes derived from bicyclic dimethoxycyclobutenes has been examined as part of a series of model studies leading toward the synthesis of the anthracyclinone antibiotics adriamycin and daunorubicin. In general, regiospecificity appears governed primarily by diene polarization factors. The structural assignments have been confirmed by a single-crystal X-ray analysis of one of the tetracyclic adducts from juglone methyl ether and related by chemical interconversion.

The development of synthetic approaches to the anthracyclinone class of antitumor antibiotics has been the object of intense study by a number of research groups in this country and abroad. The clinical importance of adriamycin (**1**) and to a lesser extent daunorubicin (**2**) as antitumor agents has been a major stimulus of this activity.[3] In addition, though, the unreliability of biochemical sources of the active substances[4] and the discovery of significant and potentially severe side effects, especially acute cardiac toxicity resulting from therapeutic administration of **1** and **2**, have further encouraged the exploration of methods to prepare not only **1** and **2** but a variety of analogues which are unavailable by chemical modification of **1** and **2**.




3

**1**, R = OH
**2**, R = H

The total synthesis of **1** and related systems poses three independent problems: (1) aglycone synthesis, (2) synthesis of the requisite carbohydrate, and (3) methodology for

(1) For previous studies see: Boeckman, Jr., R. K.; Dolak, T. M.; Culos, K. O. *J. Am. Chem. Soc.* **1978**, *100*, 7098.
(2) (a) Fellow of the Alfred P. Sloan Foundation, 1976–1980. (b) Recipient of a Career Development Award (CA-00273) from the National Cancer Institute of the National Institutes of Health (1976–1981).
(3) Henry, D. W. *ACS Symp. Ser.* **1976**, *No.* 30.
(4) Arcamone, F.; Cassinelli, G.; Fantini, G.; Grein, A.; Orezzi, P.; Pol, P.; Spalla, C. *Biotech. Bioeng.* **1969**, *11*, 1101.

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