20. Synthesis of Derivatives of (1*R**,10a*R**)-1-Azido-10-benzylidene-4-(diethylphosphono)-1,2,10,10a-tetrahydro-2-oxo-4*H*-azeto[1,2-*a*]pyrido[1,2-*d*]pyrazin-9-ylium Bromide

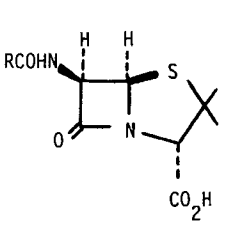
by **Gholam H. Hakimelahi*** and **Ali R. Sardarian**

Chemistry Department, Shiraz University, Shiraz, Iran

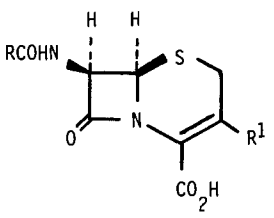
(6.VII.89)

The synthesis of some derivatives of the title compound **VI** is described. Bromination of diethyl (*cis*-3-azido-2-oxo-4-styrylazetidin-1-yl)(pyridin-2-yl)methylphosphonate (**6**) in MeOH gave tricyclic β-lactam **7**, while similar bromination of diethyl (*cis*-3-azido-2-oxo-4-vinylazetidin-1-yl)(pyridin-2-yl)methylphosphonate (**9**) afforded tricyclic β-lactam **10**. Mechanisms for these transformations are proposed (*Schemes 1* and *2*).

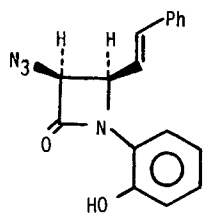
The essential features of the classical β-lactam antibiotics penicillin (**I**) and cephalosporin (**II**) are a *cis*-disubstituted β-lactam ring, an acylamino side chain, an acidic function, and a five-membered ring or a six-membered ring containing a double bond conjugated with the β-lactam N-atom conferring enough ring strain in order to render the β-lactam ring susceptible nucleophilic attack of the enzyme responsible for the bacterial cell wall synthesis. It is known that the S-atom can be replaced by an O-, N-, or C-atom without substantial loss of antimicrobial activity [1] [2]. We have shown that



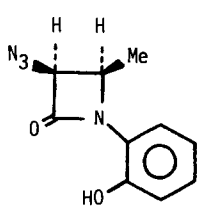
I



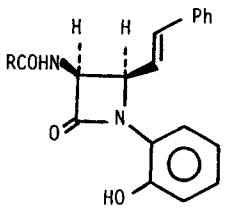
II



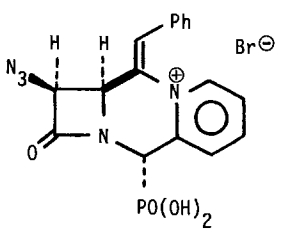
III



IV



V

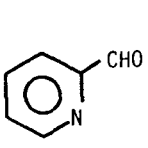


VI

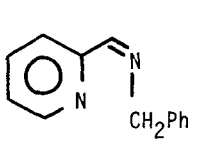
compound **III** exhibits weak antibacterial activity and good anticancer property, while **IV** and **V** display none [3].

We wish to describe now the synthesis of β-lactams similar to penicillin and cephalosporin but differing in that the COOH function is replaced by a phosphonic acid, and the strain of the β-lactam is generated by electron-withdrawing properties of an attached pyridine ring and/or by fusing this pyridine moiety to the β-lactam by means of an additional ring as indicated in structure **VI**. Furthermore, the presence of the phosphonic acid in **VI** might provide more selectivity towards tumor cells than towards normal tissues [4].

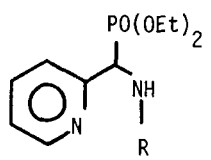
We chose as starting material the readily available pyridine-2-carbaldehyde (**1**) which was converted in nearly quantitative yield to its *Schiff* base **2** by means of benzylamine in CH_2Cl_2. Reaction with diethyl phosphite at elevated temperature afforded compound **3** (99%), and removal of the benzylic group was easily accomplished by catalytic transfer reduction [5] of **3**·HCl using $PdCl_2$ and cyclohexene in refluxing EtOH for 20 h (→ **4**; 80%). The structure of aminophosphonate **4** followed from its spectral and analytical data. Using the procedure described by *Doyle et al.* [6], **4** was transformed to its stable *Schiff* base **5** which, upon reaction with azidoacetyl chloride and Et_3N in CH_2Cl_2 at −10°, gave β-lactam **6** (80%) as a mixture of epimers at the phosphonate-bearing C-atom. All β-lactams obtained by this method were *cis*-disubstituted [7] as determined by ^{1}H-NMR ($J = 5$ Hz) of all derivatives in which the relevant protons did not overlap with other signals. Bromination of **6** with Br_2 in CH_2Cl_2 or $CHCl_3$ failed, resulting in the formation of unidentifiable compounds. However, bromination in MeOH afforded β-lactam **7** (70%) characterized by its IR, ^{1}H-NMR, mass spectra, and elemental analysis.



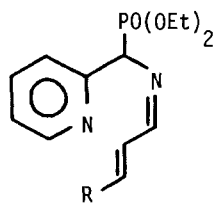
1



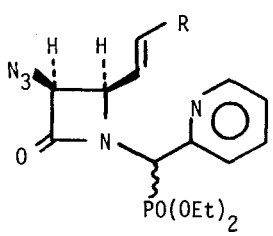
2



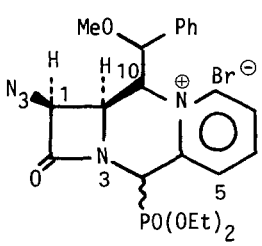
3 R = $PhCH_2$
4 R = H



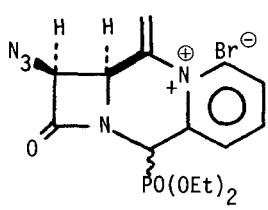
5 R = Ph
8 R = H



6 R = Ph
9 R = H



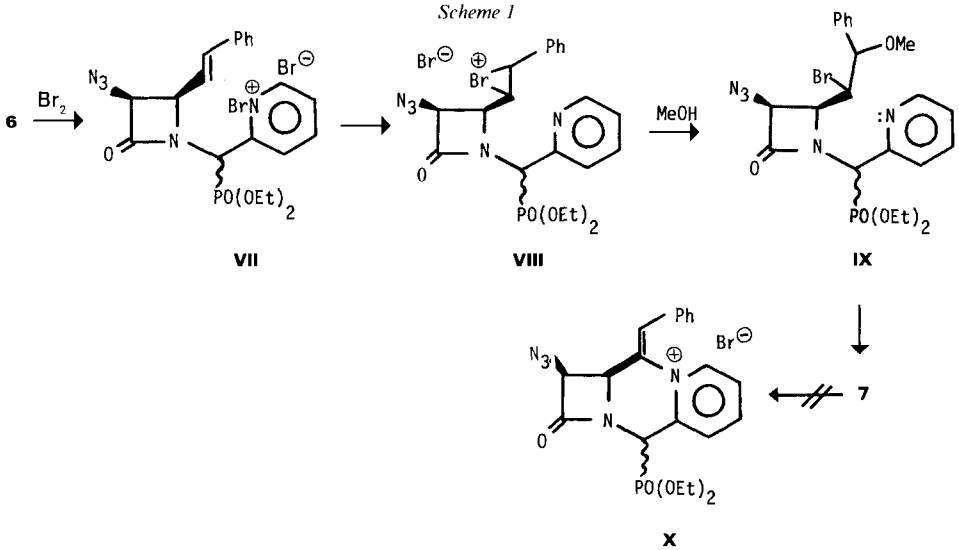
7



10

Since the benzylic position of the intermediate bromonium ion **VIII** (formed from **6** *via* **VII**) is more susceptible to solvolysis than to internal nucleophilic attack of the N-atom of the pyridine moiety, we suggest that **7** is obtained *via* **IX** according to the mechanism given in *Scheme 1*.

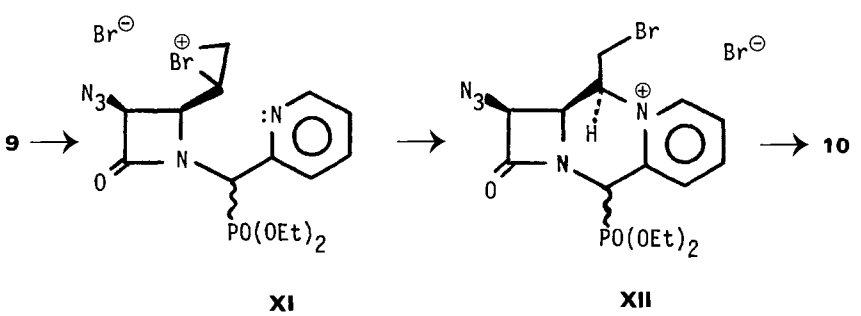
Scheme 1



All attempts (with, 1,8-diazabicyclo[5.4.0]undecan-7-one(DBU)/THF) to eliminate the MeO function in **7** to afford the desired compound **X** *(Scheme 1)* failed, resulting in the destruction of the β-lactam ring.

In order to establish the effect of the Ph substituent of the bromonium ion **VIII** on the solvolysis at its benzylic position, we performed a similar series of reactions using acrylaldehyde for the *Schiff*-base formation from **4**. Treatment of the resulting *Schiff* base **8** with azidoacetyl chloride gave *cis*-β-lactam **9** (60%), and bromination of **9** with Br_2/MeOH afforded the expected tricyclic compound **10** (*ca.* 35%), presumably by an internal nucleophilic attack of the N-atom of the pyridine ring in the intermediate bromonium ion **XI**, followed by elimination of H Br from **XII** *(Scheme 2)*. Thus, the

Scheme 2



internal nucleophilic displacement in **XI** under formation of a favorable six-membered ring is faster than the internal nucleophilic attack at the benzylic position of **VIII** *(Scheme 1)*; in the latter case, solvolysis can preferably compete with the formation of a seven-membered ring.

All attempts to deprotect the phosphonic-acid moiety [8] in **7** and **10** failed, resulting in recovery or destruction of the starting materials.

This work was supported by the *Shiraz University Research Council* and *Radja Chemical and Pharmaceutical Company*.

Experimental Part

General. See [9].

N-[(Pyridin-2-yl)methylidene]benzylamine (**2**), *Diethyl [(3-Phenylprop-2-enylidene)amino](pyridin-2-yl)-methylphosphonate* (**5**), *and Diethyl [(Prop-2-enylidene)amino](pyridin-2-yl)methylphosphonate* (**8**). *Representative Procedure*: To a soln. of **4** (2.13 g, 0.01 mol) in dry CH_2Cl_2 (250 ml) was added cinnamaldehyde (1.32 g, 0.01 mol). The soln. was brought to reflux and the CH_2Cl_2 distilled slowly under constant addition of dry CH_2Cl_2 so as to maintain the same volume of liquid. After removal of all reaction H_2O (5 h), the soln. was cooled and $MgSO_4$ added. After 1 h, the mixture was filtered and the soln. evaporated: 3.30 g (99%) of **5** as an oil. IR (CH_2Cl_2): 1636 (HC=N). ^{1}H-NMR ($CDCl_3$): 1.00–1.52 (*2t*, $2CH_3CH_2O$); 3.88–4.48 (*2q*, $2CH_3CH_2O$); 5.57 (*d*, J = 18, CHP); 6.70–8.70 (*m*, PhCH=CHCH, C_5H_4N).

8: Oil. IR (CH_2Cl_2): 1640 (HC=N). ^{1}H-NMR ($CDCl_3$): 1.01–1.52 (*2t*, $2CH_3CH_2O$); 3.89–4.48 (*2q*, $2CH_3CH_2O$); 5.54 (*d*, J = 18.6 CHP); 5.45–6.20 (*m*, CH_2=CH); 7.31 (br. *d*, CH=N); 7.01–7.70 (*m*, 3 H of Py); 8.52 (br. *d*, H_o of Py).

2: Oil. From benzylamine and pyridine-2-carbaldehyde (**1**) in CH_2Cl_2 in the presence of $MgSO_4$ at 25°. IR (CH_2Cl_2): 1650 (HC=N). ^{1}H-NMR ($CDCl_3$): 4.78 (*s*, $PhCH_2$); 6.91–8.69 (*m*, HC=N, Ph, Py).

Diethyl (cis-3-Azido-2-oxo-4-styrylazetidin-1-yl)(pyridin-2-yl)methylphosphonate (**6**) *and Diethyl (cis-3-Azido-2-oxo-4-vinylazetidin-1-yl)(pyridin-2-yl)methylphosphonate* (**9**). *Representative Procedure*: To the freshly prepared **5** (3.58 g, 0.01 mol) in dry CH_2Cl_2 (200 ml) was added at −10° Et_3N (2.02 g, 0.02 mol). A soln. of azidoacetyl chloride (1.2 g, 0.01 mol) in dry CH_2Cl_2 (30 ml) was added dropwise within 45 min. The soln. was stirred for 2.5 h and evaporated. The residue was dissolved in Et_2O, treated with charcoal, filtered, and evaporated to give, after chromatography on silica gel ($CHCl_3$), 3.12 g (80%) of **6** as an oily mixture of diastereoisomers. IR (CH_2Cl_2): 2100 (N_3), 1758 (β-lactam). ^{1}H-NMR ($CDCl_3$): 1.01–1.51 (*2t*, 2 CH_3CH_2O); 3.89–4.49 (*2q*, 2 CH_3CH_2O); 4.89 (br., H–C(4)); 5.20 (*d*, J = 19.5, CHP); 5.54 (*d*, J = 5.5, H–C(3)); 6.50 (*dd*, J = 16, 7, PhCH=C*H*); 6.72 (*d*, J = 16, PhC*H* = CH); 7.00–7.81 (*m*, Ph, 3 H of Py); 8.50 (br. *d*, H_o of Py). Anal. calc. for $C_{21}H_{24}N_5O_4P$ (441.33): C 57.14, H 5.44, N 15.87; found: C 57.19, H 5.45, N 15.89.

9: Oil (60%). IR (CH_2Cl_2): 2100 (N_3), 1755 (β-lactam). ^{1}H-NMR ($CDCl_3$): 1.00–1.50 (*2t*, $2CH_3CH_2O$); 3.80–4.31 (*2q*, 2 CH_3CH_2O); 4.73 (br., H–C(4)); 4.99–5.79 (*m*, CHP, H–C(3), CH_2=CH); 7.00–7.65 (*m*, 3 H of Py); 8.49 (br. *d*, J = 3.5, H_o of Py). Anal. calc. for $C_{15}H_{20}N_5O_4P$ (365.21): C 49.31, H 5.48, N 19.18; found: C 49.52, H 5.55, N 19.29.

Diethyl (Benzylamino)(pyridin-2-yl)methylphosphonate (**3**). To **2** (1.96 g, 0.01 mol) was added diethyl phosphite (1.40 g, 0.012 mol) at 60°. After stirring for 15 min, TLC showed the disappearance of the starting materials. Chromatography on silica gel (CH_2Cl_2/$CHCl_3$ 1:1) afforded **3** (99%) as an oil. IR (CH_2Cl_2): 3360–3380 (NH), 1580, 1600 (Ph, Py). ^{1}H-NMR ($CDCl_3$): 1.01–1.42 (*2t*, $2CH_3CH_2O$); 2.99 (br., NH, exchanged with D_2O); 3.60–4.19 (*m*, 2 CH_3CH_2O, $PhCH_2$); 4.30 (*d*, J = 18, CHP); 7.00–7.80 (*m*, Ph, 3 H of Py); 8.55 (*d*, J = 3.5, H_o of Py). Anal. calc. for $C_{17}H_{23}N_2O_3P$ (334.31): C 61.08, H 6.88, N 8.38; found: C 61.10, H 7.02, N 8.41.

Compound **3** was dissolved in Et_2O and HCl gas bubbled into the soln. After 5 min, the solvent was evaporated: **3**·HCl (100%) as a foam.

Diethyl Amino(pyridin-2-yl)methylphosphonate (**4**). Compound **3**·HCl (3.705 g, 0.01 mol) was dissolved in refluxing EtOH (400 ml). Cyclohexene (200 ml) and $PdCl_2$ (3 g) were added, and refluxing was continued for 20 h. The mixture was filtered the filtrate evaporated, and the residue chromatographed on silica gel (AcOEt): **4** (80%). IR (CH_2Cl_2): 3350–3400 (NH_2), 1580 (Py). ^{1}H-NMR ($CDCl_3$): 1.01–1.49 (*2t*, 2 CH_3CH_2O); 3.09 (br., NH_2, exchange with D_2O); 3.79–4.29 (*2q*, 2 CH_3CH_2O); 4.44 (*d*, J = 18, CHP); 7.00–7.80 (*m*, 3 H of Py); 8.55 (*d*, J = 4, H_o of Py). Anal. calc. for $C_{10}H_{17}N_2O_3$ (213.13): C 56.34, H 7.98, N 13.14; found: C 56.45, H 8.11, N 12.98.

(1R,10aR*)-1-Azido-4-(diethylphosphono)-1,2,10,10a-tetrahydro-10-(α-methoxybenzyl)-2-oxo-4H-azeto[1,2-α]pyrido[1,2-d]pyrazin-9-ylium Bromide* (**7**) *and (1R*,10aR*)-1-Azido-4-(diethylphosphono)-1,2,10,10a-tetrahydro-10-methylidene-2-oxo-4H-azeto[1,2-a]pyrido[1,2-d]pyrazin-9-ylium Bromide* (**10**). *Representative Procedure*: β-Lactam **6** (4.41 g, 0.01 mol) was dissolved in MeOH (70 ml) and Br_2 (0.012 mol) added dropwise with stirring at 25°. After 15 min, the soln. was evaporated and the residue purified by prep. TLC (Et_2O/MeOH 7:3): **7** (70%). M.p. 130–132°. IR (CH_2Cl_2): 2110 (N_3), 1769 (β-lactam). ^{1}H-NMR ($CDCl_3$): 1.09–1.62 (2*t*, $2CH_3CH_2O$); 3.49–4.11 (*m*, 2 CH_3CH_2O, H–C(10), H–C(10a)); 3.80 (*s*, CH_3O); 4.41 (*d*, J = 5.5, H–C(1)); 4.90 (br. *d*, PhC*H*); 6.10 (*d*, J = 18, H–C(4)); 7.11–7.59 (*m*, Ph); 8.62–9.35 (*m*, H–C(5), H–C(6), H–C(7)); 10.32 (*d*, J = 4, H–C(8)). Anal. calc. for $C_{22}H_{27}BrN_5O_5P$ (552.43): C 47.83, H 4.89, N 12.68, Br 14.49; found: C 47.80, H 4.91, N 12.70, Br 14.54.

10: Foam (35%). IR (CH_2Cl_2): 2100 (N_3), 1782 (β-lactam). ^{1}H-NMR ((D_6)DMSO): 1.00–1.49 (2*t*, $2CH_3CH_2O$); 3.51–4.12 (*m*, 2 CH_3CH_2O, H–C(10a)); 4.31 (*d*, J = 5, H–C(1)); 6.40 (*d*, J = 20, H–C(4), exchange with D_2O); 7.25 (br. *d*, CH_2=C); 8.41–9.25 (*m*, H–C(5), H–C(6), H–C(7)); 10.41 (br. *d*, H–C(8)). Anal. calc. for $C_{15}H_{19}BrN_5O_4P$ (444.35): C 40.54, H 4.28, N 15.77, Br 18.02; found: C 40.43, H 4.30, N 15.97, Br 18.13.

REFERENCES

[1] T.W. Doyle, B. Belleau, B.-Y. Luh, C.F. Ferrari, M.P. Cunningham, *Can. J. Chem.* **1977**, *55*, 468.
[2] R.A. Firestone, J.L. Fahey, N.S. Maciejewicz, G.S. Pater, B.G. Christensen, *J. Med. Chem.* **1977**, *20*, 551.
[3] G. Just, G.H. Hakimelahi, U.S. Patent, 4, 385, 175, May 24, 1983; G.H. Hakimelahi, unpublished results.
[4] H. Dugas, C. Penney, 'Bioorganic Chemistry, A Chemical Approach to Enzyme Action', Ed. C.R. Cantor, Springer-Verlag, Berlin, 1981, p. 36.
[5] E.A. Braude, R.P. Linstead, P.W. Mitchell, K.R.H. Woolridge, *J. Chem. Soc.* **1954**, 3595; V.S. Rao, A.S. Perlin, *Carbohydr. Res.* **1980**, *83*, 175; S. Hanessian, T.J. Liak, B. Vanasse, *Synthesis* **1981**, 396.
[6] T.W. Doyle, A. Martel, B.-y. Luh, *Can. J. Chem.* **1977**, *55*, 2708.
[7] H.B. Kagan, J.J. Basselier, J.L. Luche, *Tetrahedron Lett.* **1964**, 941.
[8] T. Morita, Y. Okamoto, H. Sakurai, *Tetrahedron Lett.* **1978**, 2523.
[9] G.H. Hakimelahi, M. Zarrinehzad, A.A. Jarrahpour, H. Sharghi, *Helv. Chim. Acta* **1987**, *70*, 219.