

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

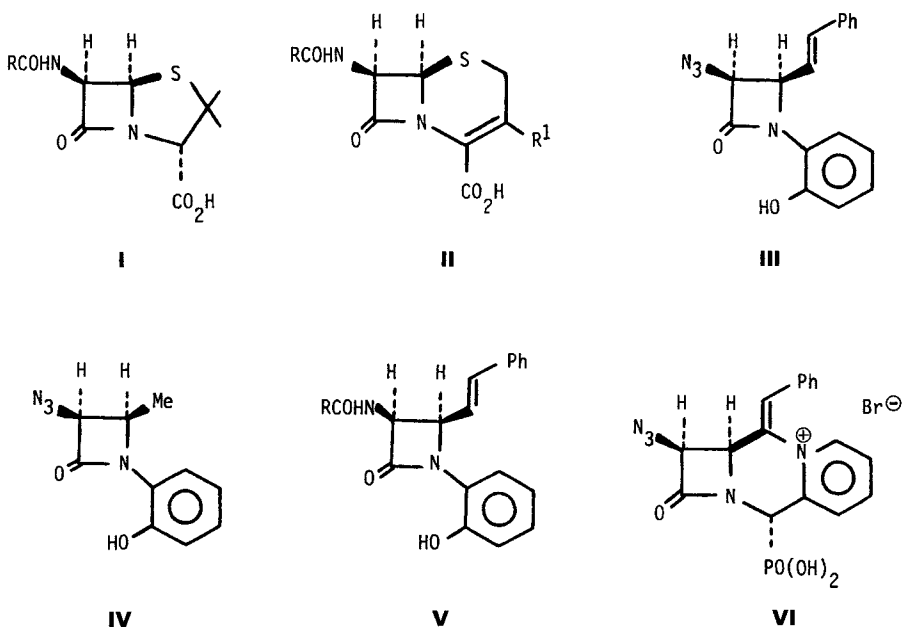
by Gholam H. Hakimelahi* and Ali R. Sardarian

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).

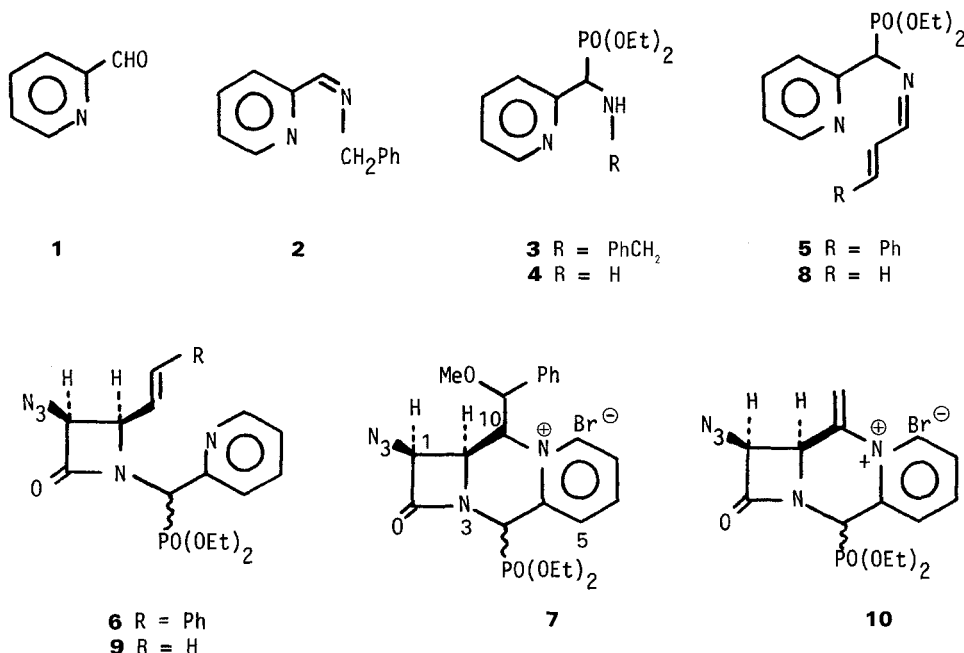
The essential features of the classical β -lactam antibiotics penicillin (**I**) and cephalosporin (**II**) are a *cis*-disubstituted β -lactam ring, an acylamino side chain, an acidic function, and a five-membered ring or a six-membered ring containing a double bond conjugated with the β -lactam N-atom 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



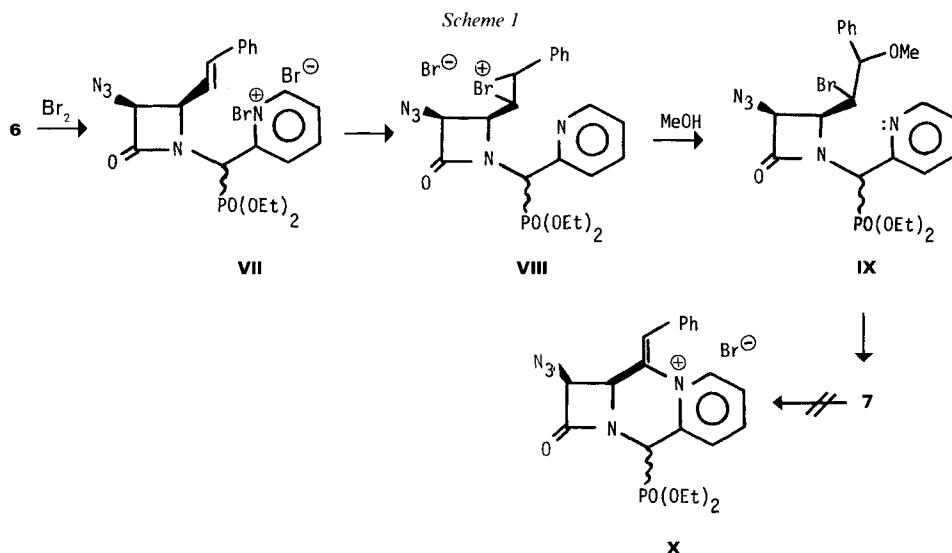
compound **III** exhibits weak antibacterial activity and good anticancer property, while **IV** and **V** display none [3].

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 ($\rightarrow$ **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 $^1\text{H-NMR}$ ($J = 5$ 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, $^1\text{H-NMR}$, mass spectra, and elemental analysis.

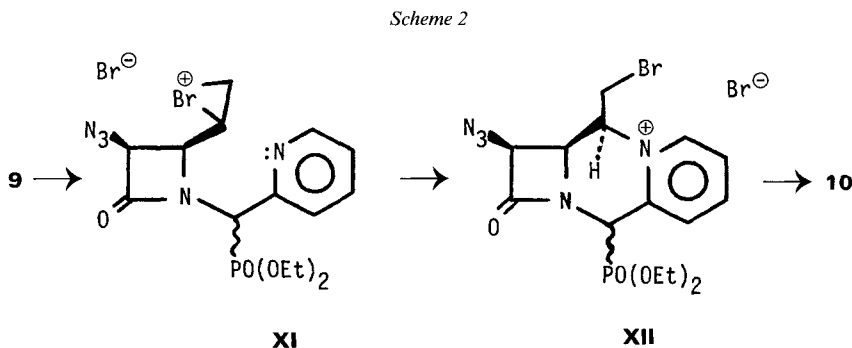


Since the benzylic position of the intermediate bromonium ion **VIII** (formed from **6** via **VII**) is more susceptible to solvolysis than to internal nucleophilic attack of the N-atom of the pyridine moiety, we suggest that **7** is obtained via **IX** according to the mechanism given in *Scheme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



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 HBr from **XII** (*Scheme 2*). Thus, the



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 ($\text{HC}=\text{N}$). $^1\text{H-NMR}$ (CDCl_3): 1.00–1.52 (2t, $2\text{CH}_3\text{CH}_2\text{O}$); 3.88–4.48 (2q, $2\text{CH}_3\text{CH}_2\text{O}$); 5.57 (d, $J = 18$, CHP); 6.70–8.70 (m, $\text{PhCH}=\text{CHCH}$, $\text{C}_5\text{H}_4\text{N}$).

8: Oil. IR (CH_2Cl_2): 1640 ($\text{HC}=\text{N}$). $^1\text{H-NMR}$ (CDCl_3): 1.01–1.52 (2t, $2\text{CH}_3\text{CH}_2\text{O}$); 3.89–4.48 (2q, $2\text{CH}_3\text{CH}_2\text{O}$); 5.54 (d, $J = 18.6$ CHP); 5.45–6.20 (m, $\text{CH}_2=\text{CH}$); 7.31 (br. d, $\text{CH}=\text{N}$); 7.01–7.70 (m, 3 H of Py); 8.52 (br. d, H_α 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 ($\text{HC}=\text{N}$). $^1\text{H-NMR}$ (CDCl_3): 4.78 (s, PhCH_2); 6.91–8.69 (m, $\text{HC}=\text{N}$, Ph, Py).

Diethyl (cis-3-Azido-2-oxo-4-styrylazetid-1-yl)(pyridin-2-yl)methylphosphonate (**6**) and Diethyl (cis-3-Azido-2-oxo-4-vinylazetid-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). $^1\text{H-NMR}$ (CDCl_3): 1.01–1.51 (2t, $2\text{CH}_3\text{CH}_2\text{O}$); 3.89–4.49 (2q, $2\text{CH}_3\text{CH}_2\text{O}$); 4.89 (br., $\text{H}-\text{C}(4)$); 5.20 (d, $J = 19.5$, CHP); 5.54 (d, $J = 5.5$, $\text{H}-\text{C}(3)$); 6.50 (dd, $J = 16$, 7, $\text{PhCH}=\text{CH}$); 6.72 (d, $J = 16$, $\text{PhCH}=\text{CH}$); 7.00–7.81 (m, Ph, 3 H of Py); 8.50 (br. d, H_α of Py). Anal. calc. for $\text{C}_{21}\text{H}_{24}\text{N}_5\text{O}_4\text{P}$ (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). $^1\text{H-NMR}$ (CDCl_3): 1.00–1.50 (2t, $2\text{CH}_3\text{CH}_2\text{O}$); 3.80–4.31 (2q, $2\text{CH}_3\text{CH}_2\text{O}$); 4.73 (br., $\text{H}-\text{C}(4)$); 4.99–5.79 (m, CHP, $\text{H}-\text{C}(3)$, $\text{CH}_2=\text{CH}$); 7.00–7.65 (m, 3 H of Py); 8.49 (br. d, $J = 3.5$, H_α of Py). Anal. calc. for $\text{C}_{15}\text{H}_{20}\text{N}_5\text{O}_4\text{P}$ (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 ($\text{CH}_2\text{Cl}_2/\text{CHCl}_3$ 1:1) afforded **3** (99%) as an oil. IR (CH_2Cl_2): 3360–3380 (NH), 1580, 1600 (Ph, Py). $^1\text{H-NMR}$ (CDCl_3): 1.01–1.42 (2t, $2\text{CH}_3\text{CH}_2\text{O}$); 2.99 (br., NH, exchanged with D_2O); 3.60–4.19 (m, $2\text{CH}_3\text{CH}_2\text{O}$, 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_α of Py). Anal. calc. for $\text{C}_{17}\text{H}_{23}\text{N}_2\text{O}_3\text{P}$ (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). $^1\text{H-NMR}$ (CDCl_3): 1.01–1.49 (2t, $2\text{CH}_3\text{CH}_2\text{O}$); 3.09 (br., NH_2 , exchange with D_2O); 3.79–4.29 (2q, $2\text{CH}_3\text{CH}_2\text{O}$); 4.44 (d, $J = 18$, CHP); 7.00–7.80 (m, 3 H of Py); 8.55 (d, $J = 4$, H_α of Py). Anal. calc. for $\text{C}_{10}\text{H}_{17}\text{N}_2\text{O}_3$ (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-ylum Bromide (**7**) and (1R*,10aR*)-1-Azido-4-(diethylphosphono)-1,2,10,10a-tetrahydro-10-methylidene-2-oxo-4H-azeto[1,2- α]pyrido[1,2-d]pyrazin-9-ylum Bromide (**10**). *Representative Procedure*: β -Lactam **6** (4.41 g, 0.01 mol) was dissolved in MeOH (70 ml) and Br₂ (0.012 mol) added dropwise with stirring at 25°. After 15 min, the soln. was evaporated and the residue purified by prep. TLC (Et₂O/MeOH 7:3): **7** (70%). M.p. 130–132°. IR (CH₂Cl₂): 2110 (N₃), 1769 (β -lactam). ¹H-NMR (CDCl₃): 1.09–1.62 (2t, 2CH₃CH₂O); 3.49–4.11 (m, 2 CH₃CH₂O, H–C(10), H–C(10a)); 3.80 (s, CH₃O); 4.41 (d, *J* = 5.5, H–C(1)); 4.90 (br. d, PhCH); 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 C₂₂H₂₇BrN₅O₅P (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 (CH₂Cl₂): 2100 (N₃), 1782 (β -lactam). ¹H-NMR ((D₆)DMSO): 1.00–1.49 (2t, 2 CH₃CH₂O); 3.51–4.12 (m, 2 CH₃CH₂O, H–C(10a)); 4.31 (d, *J* = 5, H–C(1)); 6.40 (d, *J* = 20, H–C(4), exchange with D₂O); 7.25 (br. d, CH₂=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 C₁₅H₁₉BrN₅O₄P (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. Zarrinehazad, A. A. Jarrahpour, H. Sharghi, *Helv. Chim. Acta* **1987**, *70*, 219.