Studies on Lactams. Part 45.[1] Some Carbocyclic Analogues of Cephalosporin [1]

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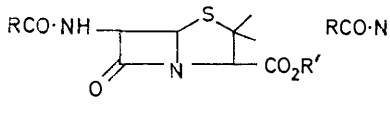
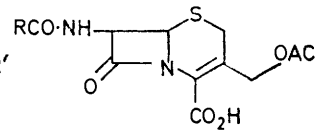
Several polycyclic β-lactams have been synthesized by the reactions of cyclic imines with acid chlorides in the presence of triethylamine. The azido-functions in these β-lactams were reduced to amino-groups, which were then acylated with phenylacetyl chloride to introduce the penicillin G side chain. Some carbocyclic analogues of cephalosporin were found to possess antibacterial activity.

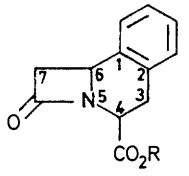
DURING studies on monocyclic β-lactams it was discovered that some compounds of this type showed antibacterial activity.[2] No structure–activity relationship was obvious on the basis of the available data. However, not all the structural features considered essential for antibiotic activity [3] in penicillins (1a) and cephalosporins (1b) were present in these monocyclic analogues. We therefore proceeded to investigate some other β-lactam structures that were not closely analogous to penicillins and cephalosporins.



(1a)



(1b)



(2)

For mechanistic purposes an S atom is often considered to be the equivalent of a C=C bond. On this basis the synthesis of polycyclic β-lactams derived from the ring system (2) was undertaken for studies of antibacterial activity.

Annelation of imines with acid chlorides and triethylamine [4] was the method employed. The imines (3)—(9) were prepared by Bischler–Napieralski cyclization of the corresponding amides (obtained from acylation of phenethylamine or homoveratrylamine with an appropriate acid chloride). During cyclization of *N*-phenethyl-*p*-cyanobenzamide with phosphoryl chloride–phosphorus pentaoxide it was observed that if the reactants were cooled before work-up the cyano-imine (3) was formed. However, if the reactants were decomposed without cooling the cyano-group was hydrolysed and only the carboxy-imine (4) was isolated. The reaction of the cyclic imine (3) with methoxyacetyl chloride in the presence of triethylamine resulted in the β-lactam (10). Under similar conditions with appropriate acid chlorides the β-lactams (10)—(14) and (23)—(28) were obtained in *ca.* 60—70% yield.

β-Lactams substituted by a free carboxy-group can be synthesized conveniently by the acid chloride–imine method if a silyl ester is used as intermediate. In order to prepare the carboxy-β-lactam (15), the carboxy-function of the imine (4) was first converted into the

[1] Part 44, A. K. Bose and M. S. Manhas, *J. Heterocyclic Chem.*, 1976, **13**, S43.

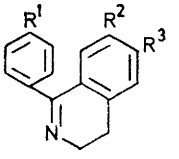
[2] A. K. Bose, J. C. Kapur, S. D. Sharma, S. G. Amin, and M. S. Manhas, *J. Medicin. Chem.*, 1974, **17**, 541; see also J. N. Wells and O. R. Tarwater, *ibid.*, 1971, **14**, 242.

[3] (*a*) M. S. Manhas and A. K. Bose, 'Synthesis of Penicillin, Cephalosporin C, and Analogs,' Dekker, New York, 1969; (*b*) M. S. Manhas and A. K. Bose, 'beta-Lactams, Natural and Synthetic,' Part I, Wiley–Interscience, New York, ch. 2; (*c*) 'Cephalosporin and Penicillin, Chemistry and Biology,' ed. E. H. Flynn, Academic Press, New York, 1972.

[4] (*a*) J. C. Sheehan and J. J. Ryan, *J. Amer. Chem. Soc.*, 1951, **73**, 1204; (*b*) A. K. Bose, B. Anjaneyulu, S. K. Bhattacharya, and M. S. Manhas, *Tetrahedron*, 1967, **23**, 4769.

silyl ester *in situ* with trimethylsilyl chloride and triethylamine in benzene solution at room temperature. The silylated imine was treated with methoxyacetyl chloride and an equivalent quantity of triethylamine, and the resulting silylated β-lactam [5] on treatment with methanol afforded the carboxy-β-lactam (15).

The azido-β-lactams (12)—(14) and (26)—(28) were catalytically (10% Pd–C) reduced to the corresponding amino-β-lactams (17)—(19) and (29)—(31). Similarly, the nitro-group in the β-lactam (11) was also reduced catalytically to yield the β-lactam (16). The penicillin G side chain could be incorporated easily by acylating these amino-β-lactams. Thus treatment of compounds (17)—(19), (29), and (31) with phenylacetyl chloride

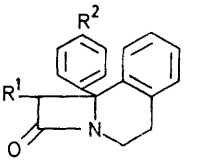


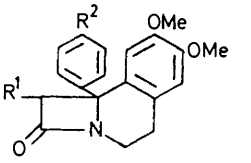
	R^1	R^2	R^3
(3)	CN	H	H
(4)	CO_2H	H	H
(5)	Me	H	H
(6)	OMe	H	H
(7)	NO_2	H	H
(8)	CN	OMe	OMe
(9a)	Br	OMe	OMe
(9b)	OMe	OMe	OMe

gave the amido-β-lactams (20)—(22), (32), and (33), respectively.

In order to introduce the carboxy-function into the carbocyclic β-lactams, to obtain structures of type (2), the synthesis of the imine (37) was undertaken. The readily available starting material, *N*-[α-carboxy-β-(4-hydroxy-3-methoxyphenyl)ethyl]benzamide (34), was refluxed with dimethyl sulphate (2 mol. equiv.) in dry benzene in the presence of anhydrous potassium carbonate to obtain the corresponding dimethoxy-ester (36) in 80% yield. Alternatively, methylation of (34) with diazomethane gave the hydroxy-ester (35) which could be converted into (36) with dimethyl sulphate. The amido-ester (36) was cyclized to the imine (37) with phosphorus pentaoxide and phosphoryl chloride. However when the benzyloxy-benzyl ester (42) was treated similarly no cyclization to the imine (43) took place.

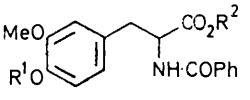
The reaction of phenoxyacetyl chloride with the imine (37) and triethylamine in dichloromethane gave the β-lactam (38) as a single isomer. Similarly azidoacetyl chloride and (37) produced the azido-derivative (39), which was catalytically reduced to the α-amino-β-lactam (40). Acylation of (40) with phenylacetyl chloride in the presence of triethylamine produced the amido-compound (41). Attempts to hydrolyse the methyl ester (38) to the corresponding free acid β-lactam



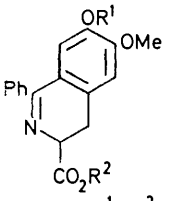


	R^1	R^2		R^1	R^2
(10)	OMe	CN	(23)	OMe	Br
(11)	OMe	NO_2	(24)	OPh	Br
(12)	N_3	Me	(25)	OPh	CN
(13)	N_3	OMe	(26)	N_3	Br
(14)	N_3	H	(27)	N_3	CN
(15)	OMe	CO_2H	(28)	N_3	OMe
(16)	OMe	NH_2	(29)	NH_2	Br
(17)	NH_2	Me	(30)	NH_2	CN
(18)	NH_2	OMe	(31)	NH_2	OMe
(19)	NH_2	H	(32)	$NH{\cdot}CO{\cdot}CH_2Ph$	Br
(20)	$NH{\cdot}CO{\cdot}CH_2Ph$	Me	(33)	$NH{\cdot}CO{\cdot}CH_2Ph$	OMe
(21)	$NH{\cdot}CO{\cdot}CH_2Ph$	OMe			
(22)	$NH{\cdot}CO{\cdot}CHCl_2$	H			

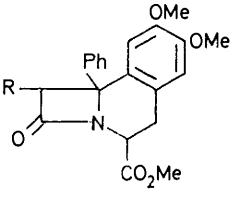
by treatment with lithium iodide–pyridine [6] or lithium iodide–dimethylformamide–sodium acetate [7] were unsuccessful.



(34) $R^1 = R^2 = H$
(35) $R^1 = H$, $R^2 = Me$
(36) $R^1 = R^2 = Me$
(42) $R^1 = R^2 = CH_2Ph$



(37) $R^1 = R^2 = Me$
(43) $R^1 = R^2 = CH_2Ph$



(38) R = OPh
(39) R = N_3
(40) R = NH_2
(41) R = $NH{\cdot}CO{\cdot}CH_2Ph$

The reactions of acid chlorides with the imines could theoretically give two β-lactams with *cis*- and *trans*-configurations. In all these reactions only a single isomer was formed, as revealed by t.l.c. of the crude

[5] A. K. Bose, S. D. Sharma, J. C. Kapur, and M. S. Manhas, *Synthesis*, 1973, 216.

[6] F. Elsinger, *Org. Synth.*, 1965, **45**, 7.

[7] J. E. McMurray and G. B. Wong, *Synth. Comm.*, 1972, **2**, 389.

product or spectroscopic analysis. On the basis of the available spectroscopic data it is not feasible to assign relative stereochemistry to the substituents at C-6 and C-7.

The β-lactams described here were extensively screened for antibacterial activity against a variety of gram-positive and gram-negative bacteria. Most did not show appreciable activity.[8] However, a few were active at a dose level of 50—100 μg ml^{-1} (see Table 1).

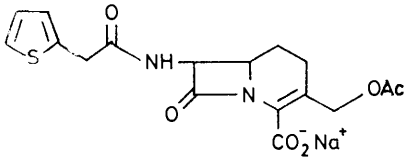
TABLE 1

Antibacterial activity of β-lactams *

Compd.	Organism	MIC * (μg mol^{-1})
(16)	*Diplococcus pneumoniae* L54	100
	Pasteurella multocida A273	100
(38)	*Brucella melitensis* A 1 030 (gram neg.)	100
	Klebsiella pneumoniae A 809 (gram neg.)	50
	Shigella equirulis T3 (gram neg.)	50
(39)	*Brucella melitensis* A488 (gram neg.)	50
	Shigella equirulis T3 (gram neg.)	50

* A stock solution of the test compounds at a concentration of 2 000 μg ml^{-1} in 0.05M-phosphate buffer at pH 6.5 was prepared and two-fold dilutions were made with sterile buffer. Quantities (1 ml) of each dilution were then incorporated into brain heat infusion agar (19 ml) in sterile petri dishes. The hardened surface was then incubated for 18 h at 37 °C. The minimum inhibitory concentration (MIC) was determined.

Unfortunately, the corresponding free carboxy-compounds were not available. Conversion of the azido-group in (39) to an amino- (40) or amido- (41) function eliminates all activity. A recently described [9] carbocyclic analogue (42) of the cephalosporins exhibits good antibacterial activity.



(42)

EXPERIMENTAL

M.p.s were determined for samples in open capillary tubes with a Mel-Temp apparatus. I.r. spectra were obtained with a Perkin-Elmer Infracord spectrometer. N.m.r. spectra were recorded with a Varian A-60A spectrometer operating at 60 MHz with tetramethylsilane as internal standard. Mass spectra were obtained with a Perkin-Elmer RMU-7 spectrometer. Elemental analyses were performed by A. Bernhardt, Max-Planck Institute, Mülheim, West Germany, and Central Drugs Research Institute, Lucknow, India.

Azidoacetyl chloride was prepared by the method of Bertho and Maier.[10] Phenoxyacetyl chloride and methoxyacetyl chloride were procured from Aldrich Chemical Co.

N-[α-Methoxycarbonyl-β-(4-hydroxy-3-methoxyphenyl)-ethyl]benzamide (35).—*N*-[α-Carboxy-β-(4-hydroxy-3-methoxyphenyl)ethyl]benzamide (34) (10 g, 0.031 mol) was added to a solution of diazomethane in dry ether and left overnight. Removal of the solvent under reduced pressure gave the *ester* (35) (8.4 g, 80%), m.p. 132—133° (from benzene), $\nu_{max.}$ (Nujol) 3 430 (OH), 3 300 (NH), 1 730 (ester CO), and 1 650 cm^{-1} (amide CO); δ($CDCl_3$) 3.2 (2 H, d), 3.76 (6 H, s), 5.03 (1 H, m), and 6.5—7.83 (9 H, m); M^+ 329 (Found: C, 65.7; H, 5.65; N, 3.9. $C_{18}H_{19}NO_5$ requires C, 65.6; H, 5.8; N, 4.2%).

N-[β-(3,4-Dimethoxyphenyl)-α-methoxycarbonylethyl] benzamide (36).—(*a*) A mixture of the hydroxy-acid (34) (10 g, 0.031 mol), anhydrous potassium carbonate (20 g, 0.155 mol), and dimethyl sulphate (8.0 g, 0.064 mol) in dry benzene was refluxed for 3 h, then filtered. The residue was washed with benzene and the combined benzene extracts were concentrated under vacuum to provide the *dimethoxy-ester* (36) (10.0 g, 91%), m.p. 98—100° (from hexane–methylene chloride); $\nu_{max.}$ (Nujol) 3 300 (NH), 1 740 (ester CO), and 1 640 cm^{-1} (amide CO); δ($CDCl_3$) 3.11 (2 H, d), 3.76 (6 H, s), 3.85 (3 H, s), 5.08 (1 H, m), and 6.55—7.86 (9 H, m) (Found: C, 66.3; H, 6.05; N, 4.12. $C_{19}H_2NO_5$ requires C, 66.45; H, 6.1; N, 6.1%).

(*b*) The hydroxy-ester (35) (4.6 g) was treated with dimethyl sulphate as under (*a*) to produce the methoxy-ester (36) (3.5 g, 73%), m.p. 98—100°.

General Method for the Synthesis of 3,4-Dihydroisoquinolines.—An illustrative example is given.

Methyl 3,4-dihydro-6,7-dimethoxy-1-phenylisoquinoline-3-carboxylate (37). The benzamide (36) (6.0 g, 0.0175 mol), phosphoryl chloride (6.7 g, 0.43 mol), and phosphorus pentaoxide (7.5 g, 0.052 mol) were refluxed in xylene with stirring for 3 h, and after cooling to 25 °C water was added. The organic phase was removed and the aqueous phase neutralized with sodium hydroxide (30%). The aqueous layer was extracted with chloroform (3 × 100 ml) and the

TABLE 2

3,4-Dihydroisoquinolines

Compd.	M.p. (°C)	Yield (%)	Spectral data
(3)	146—147	55	$\nu_{max.}$ 2 205 and 1 600 cm^{-1}; δ 2.6—2.95 (2 H, m), 3.8—4.0 (2 H, m), 7.0—7.35 (4 H, m), and 7.6 (4 H, s); M^+ 232
(4)	233—235	45	$\nu_{max.}$ 3 350, 1 720, and 1 610 cm^{-1}; δ 2.7—3.0 (2 H, m,) 3.4—3.7 (2 H, m), 7.2 (4 H, s), and 7.7—7.95 (4 H, m); M^+ 251
(5)	75—76	65	$\nu_{max.}$ 1 605 cm^{-1}; δ 2.35 (3 H, s), 2.42—2.75 (2 H, m), 3.5—3.8 (2 H, m), 7.5 (4 H, d, *J* 7 Hz), and 7.1—7.35 (4 H, m); M^+ 235
(6)	94—95	70	$\nu_{max.}$ 1 610 cm^{-1}; δ 2.65—2.9 (2 H, m), 2.75—4.0 (5 H, m), and 6.85—7.8 (8 H, m); M^+ 237
(7)	118—120	60	$\nu_{max.}$ 1 610 cm^{-1}; δ 2.7—3.0 (2 H, m), 3.8—4.1 (2 H, m), and 7.1—8.3 (8 H, m); M^+ 257
(8)	134—135	60	$\nu_{max.}$ 2 210 and 1 600 cm^{-1}; M^+ 292
(9a)	142—143	68	$\nu_{max.}$ 1 620 cm^{-1}; δ 2.65—2.9 (2 H, m), 3.7—4.0 (8 H, m), 6.8 (2 H, s), and 7.6 (4 H, s); M^+ 346
(9b)	118—119	65	$\nu_{max.}$ 1 620 cm^{-1}; M^+ 297

[8] Also see (*a*) J. N. Wells and O. R. Tarwater, *J. Medicin. Chem.*, 1971, **14**, 242; (*b*) R. F. Abdulla and K. H. Fuhr, *ibid.*, 1975, **18**, 625; (*c*) H. Vanderhaeghe and J. Thomis, *ibid.*, 1975, **18**, 486.

[9] R. N. Guthikonda, L. D. Cama, and B. G. Christensen, *J. Amer. Chem. Soc.*, 1974, **96**, 7584.

[10] A. Bertho and J. Maier, *Annalen*, 1932, **498**, 52.

TABLE 3

β-Lactams

Compd.	M.p. (°C)	Yield (%)	Formula	Analysis (%) * C	H	N	Spectral data
(10)	130	60	$C_{19}H_{16}N_2O_2$	74.8 (75.0)	5.3 (5.5)	9.4 (9.2)	$\nu_{max.}$ 1 750 and 2 242 cm^{-1}; δ 2.62—2.8 (2 H, m), 3.26 (3 H, s), 35—3.75 (2 H, m), 4.75 (1 H, s), and 7 12—7.66 (8 H, m)
(11)	160	70	$C_{18}H_{16}N_2O_4$	66.25 (66.65)	4.95 (4.95)	8.65 (8.65)	$\nu_{max.}$ 1 750 cm^{-1}; δ 2.6—3.1 (2 H, m), 3.3 (3 H, s), 3.6—3.9 (2 H, m), 4.73 (1 H, s), and 7.35—8.35 (8 H, m); M^+ 324
(12)	97—98	65	$C_{18}H_{16}N_4O$				$\nu_{max.}$ 1 755 and 2 100 cm^{-1}; δ 2.3 (3 H, s), 2.45—2.8 (2 H, m), 3.5—3.8 (2 H, m), 4.82 (1 H, s), and 7.0—7.5 (8 H, m)
(13)	88—89	63	$C_{18}H_{16}N_4O_2$				$\nu_{max.}$ 1 760 and 2 100 cm^{-1}; δ 2.6—2.8 (2 H, m), 3.6—3.8 (2 H, m), 3.8 (3 H, s), 4.84 (1 H, s), and 6.8—7.6 (8 H, m), *m/e* 320 (M^+) 294, 237, 206, and 130
(14) [4c]	124—124	55	$C_{17}H_{14}N_4O$				
(15)	195—196	50	$C_{19}H_{17}NO_4$				$\nu_{max.}$ 1 745 and 1 692 cm^{-1}; δ 2.6—2.8 (2 H, m), 3.25 (3 H, s), 3.45—3.85 (2 H, m), 4.88 (1 H, s), 7.1—8.02 (8 H, m), and 10.7br (1 H)
(16)	190—192	80	$C_{18}H_{18}N_2O_2$	73.4 (73.45)	5.95 (6.15)	9.4 (9.5)	$\nu_{max.}$ 1 735 and 3 450 cm^{-1}; δ 2.5—2.8 (2 H, m), 3.13 (3 H, s), 3.4—3.8 (4 H, m), 4.66 (1 H, s), and 6.4—7.5 (8 H, m)
(17)	152—154	60	$C_{18}H_{18}N_2O$	77.6 (77.65)	6.55 (6.5)	10.1 (10.05)	$\nu_{max.}$ 1 735 and 3 350 cm^{-1}; δ 2.3 (3 H, s), 2.55—2.8 (2 H, m), 3.5—3.8 (2 H, m), 4.5br (2 H), 4.9 (1 H, s,) and 7.0—7.5 (8 H, m); M^+ 278
(18)		60	$C_{18}H_{18}N_2O_2$				$\nu_{max.}$ 1 740 and 3 320 cm^{-1}
(19) [4b]		55	$C_{18}H_{16}N_2O$				
(20)	168—169	75	$C_{26}H_{24}N_2O_2$	78.4 (78.25)	6.05 (6.1)	7.5 (7.05)	$\nu_{max.}$ 1 730 and 1 665 cm^{-1}; δ 2.4 (3 H, s), 2.65—2.85 (2 H, m), 3.35 (2 H, s), 3.5—3.8 (2 H, m), 5.5 (1 H, d, *J* 7 Hz), 6.8—7.5 (13 H, m), and 8.1 (1 H, d, *J* 7 Hz)
(21)	189—190	72	$C_{26}H_{24}N_2O_3$	75.55	5.85		$\nu_{max.}$ 1 705 and 1 750 cm^{-1}; *m/e* 293, 237, and 165
(22)	187—189	55	$C_{19}H_{16}Cl_2N_2O_2$	(75.7)	(5.85)		$\nu_{max.}$ 1 750 and 1 710 cm^{-1}; δ 2.54—2.82 (2 H, m), 3.6—3.82 (2 H, m), 5.32 (1 H, d, *J* 7 Hz), 5.7 (1 H, s), and 7.13—8.12 (10 H, m)
(23)	208—209	50	$C_{20}H_{20}BrNO_4$				$\nu_{max.}$ 1 750 cm^{-1}; δ 2.5—2.86 (2 H, m), 3.45—3.7 (2 H, m), 3.89 (3 H, s), 3.95 (3 H, s), 4.69 (1 H, s), and 6.7—7.6 (6 H, m); M^+ 419/417
(24)	172—173	75	$C_{25}H_{22}BrNO_3$	62.8 (62.5)	4.9 (4.6)	3.1 (2.9)	$\nu_{max.}$ 1 750 cm^{-1}; δ 2.6—2.83 (2 H, m), 3.52—3.82 (2 H, m), 3.85 (3 H, s), 3.9 (3 H, s), 5.5 (1 H, s), and 6.8—7.6 (11 H, m); M^+ 481/479
(25)	157—158	75	$C_{26}H_{22}N_2O_4$	73.5 (73.25)	5.15 (5.2)	6.9 (6.55)	$\nu_{max.}$ 1 765 and 2 120 cm^{-1}; δ 2.54—2.83 (2 H, m), 3.55—3.8 (2 H, m), 3.85 (3 H, s), 3.9 (3 H, s), 4.56 (1 H, s), and 6.85—7.6 (11 H, m); *m/e* 426 (M^+) 334 and 293
(26)	149—150	60	$C_{18}H_{17}BrN_4O_3$	53.05 (53.15)	4.1 (3.95)	12.9 (13.05)	$\nu_{max.}$ 1 795 and 2 100 cm^{-1}; δ 2.75 (2 H, m), 3.70 (2 H, m), 3.90 (3 H, s), 3.98 (3 H, s), 4.87 (1 H, s), 6.75 (1 H, s), 6.58 (1 H, s), and 7.70—7.18 (4 H, m); *m/e* 346, 295, 245, 181, and 134
(27)	139—140	63	$C_{20}H_{17}N_5O_3$				$\nu_{max.}$ 1 780 and 2 125 cm^{-1}; δ 2.57—2.85 (2 H, m), 3.57—3.87 (2 H, m), 3.87 (3 H, s), 3.98 (3 H, s), 4.93 (1 H, s), 6.83 (1 H, s), 7.0 (1 H, s), and 7.63 (4 H, q, *J* 7 Hz); *m/e* 347, 292, and 245
(28)	142—143	55	$C_{20}H_{20}N_4O_4$				$\nu_{max.}$ 1 700 and 2 100 cm^{-1}; δ 2.68—2.93 (2 H, m), 3.6—3.78 (2 H, m), 3.81 (3 H, s), 3.85 (3 H, s), 4.02 (3 H, s), 4.85 (1 H, s), and 6.8—7.6 (6 H, m); *m/e* 352, 294, 282, and 266
(29)	115—120	80	$C_{19}H_{19}BrN_2O_3$				$\nu_{max.}$ 1 745 and 3 340 cm^{-1}; δ 2.25br (2 H), 2.6—3.07 (2 H, m), 3.48—3.75 (2 H, m), 3.85 (3 H, s), 3.92 (3 H, s), 4.03 (1 H, s), and 6.65—7.6 (6 H, m), *m/e* 345, 207, and 164
(30)	173—175	60	$C_{20}H_{19}N_3O_3$				$\nu_{max.}$ 1 740 and 2 210 cm^{-1}; δ 2.27—2.82 (2 H, m), 3.4br (2 H), 3.52—3.8 (2 H, m), 3.84 (3 H, s), 3.94 (3 H, s), 5.5 (1 H, s), 7.0 (1 H, s), 7.2 (1 H, s), and 7.52 (4 H, q, *J* 8 Hz); *m/e* 349, 292, 277, 262, and 247
(31)	116—118	55	$C_{20}H_{22}N_2O_4$				$\nu_{max.}$ 1 760 and 3 330 cm^{-1}; δ 1.5—1.8br (2 H), 2.5—2.85 (2 H, m), 3.5—3.8 (2 H, m), 3.8 (3 H, s), 3.85 (3 H, s), 3.95 (3 H, s), 4.45 (1 H, s), and 6.65—7.35 (6 H, m); M^+ 354
(32)	177—178	75	$C_{26}H_{25}BrN_2O_4$	62.25 (62.4)	5.2 (5.8)	5.4 (5.4)	$\nu_{max.}$ 1 785 and 1 655 cm^{-1}; δ 2.68 (2 H, m), 3.39 (2 H, m), 3.62 (2 H, m), 3.99 (3 H, s), 4.08 (3 H, s), 5.43 (1 H, d, *J* 8 Hz), 6.8—7.6 (11 H, m), and 8.1 (1 H, d, *J* 8 Hz)
(33)	210—211	78	$C_{26}H_{24}N_2O_3$	71.0 (71.15)	6.15 (5.95)		$\nu_{max.}$ 1 740 and 1 689 cm^{-1}; δ 2.52—2.8 (2 H, m), 3.38 (2 H, s), 3.52—3.81 (2 H, m), 3.81 (3 H, s), 3.86 (3 H, s), 4.06 (3 H, s), 5.4 (1 H, d, *J* 9 Hz), and 6.7—7.38 (11 H, m); *m/e* 291, 275, and 237
(39)	152—153	45	$C_{21}H_{20}N_4O_5$	61.7 (61.75)	5.05 (4.95)	13.75 (13.7)	$\nu_{max.}$ 1 780 and 2 200 cm^{-1}; δ 2.09 (2 H, m), 3.88 (6 H, s), 4.0 (3 H, s), 4.4 (1 H, m), 4.87 (1 H, s), 6.75 (1 H, s), 7.04 (1 H, s), and 7.2—7.8 (5 H, m); M^+ 408

* Required values in parentheses.

extracts were dried ($MgSO_4$) and evaporated to afford the *isoquinoline* (37) (2 g, 34%), m.p. 119—120°; $\nu_{max.}$ (Nujol) 1 705 (ester CO) and 1 610 cm^{-1} (C=N); δ($CDCl_3$) 3.04 (2 H, d, *J* 10 Hz),† 3.72 (3 H, s), 3.82 (3 H, s), 3.9 (3 H, s), 4.41 (1 H, t, *J* 10 Hz),* 6.82 (2 H, s), and 7.2—7.3 (5 H, m); M^+ 325 (Found: C, 70.3; H, 6.0; N, 4.3. $C_{19}H_{19}NO_4$ requires C, 70.15; H, 5.6; N, 4.1%).

The cyclic imines (3)—(9) were similarly obtained from the corresponding *N*-acetylated β-arylethylamines (Table 2).

General Method for the Synthesis of β-Lactams.—An illustrative example is given.

Methyl 1,4,5,9b-*tetrahydro*-7,8-*dimethoxy*-2-*oxo*-1-*phenoxy*-9a-*phenyl*-2H-*azeto*[2,1-a]*isoquinoline*-4-*carboxylate* (38). Phenoxyacetyl chloride (3.1 g, 0.018 5 mol) in dry dichloromethane (100 ml) was added dropwise to a stirred solution of the dihydroisoquinoline (37) (6.0 g, 0.018 5 mol) and triethylamine (2.0 g, 0.018 5 mol) in dichloromethane (300 ml) under nitrogen. After stirring overnight at room temperature the product was poured into ice–water. The organic phase was separated, washed with water (3 × 100), dried ($MgSO_4$), and evaporated to leave the *β-lactam* (38) (2.54 g, 60%), m.p. 204—205°; $\nu_{max.}$ (Nujol) 1 765 (β-lactam CO) and 1 740 cm^{-1} (ester CO); δ($CDCl_3$) 2.4—3.22 (2 H, m), 3.82 (3 H, s), 3.9 (6 H, s), 4.5 (1 H, q, *J* 6 Hz), 5.6 (1 H, s), and 6.8—7.01 (12 H, m); M^+ 459 (Found: C, 70.9; H, 5.55; N, 3.2. $C_{27}H_{25}NO_6$ requires C, 70.6; H, 5.5; N, 3.05%).

The β-lactams (10)—(15), (23)—(28), and (39) were prepared similarly (see Table 3).

Methyl 1-*Amino*-1,4,5,9b-*tetrahydro*-7,8-*dimethoxy*-2-*oxo*-9-*phenyl*-2H-*azeto*[2,1-a]*isoquinoline*-4-*carboxylate* (40).—Small pieces of aluminium amalgam [from aluminium foil (5.0 g) and mercury(II) chloride (6 × 2 g) dissolved in water (600 ml)] were added to a stirred solution of the azido-β-lactam (39) (2.0 g, 0.005 mol) in tetrahydrofuran (100 ml), methanol (90 ml), and water (10 ml). After stirring for 4 h, the product was filtered and the residue washed with dichloromethane. The combined organic layer was washed with water, dried ($MgSO_4$), and evaporated to leave the amino-β-lactam (40) (1.4 g, 75%), m.p. 180—182°; $\nu_{max.}$ (Nujol) 3 400 (NH_2), 1 755 (β-lactam CO), and 1 735 cm^{-1} (ester CO); M^+ 382.

The amino β-lactams (17)—(20), (30), and (31) were also obtained by reduction of the corresponding azido-compounds (Table 3).

Methyl 1,4,5,9b-*Tetrahydro*-7,8-*dimethoxy*-2-*oxo*-9a-*phenyl*-1-*phenylacetamido*-2H-*azeto*[2,1-a]*isoquinoline*-4-*carboxylate* (41).—Phenylacetyl chloride (0.405 7 g, 0.002 62 mol) in dry dichloromethane (50 ml) was added dropwise to a stirred solution of the amino-β-lactam (40) (1 g, 0.002 62 mol) and triethylamine (0.29 g, 0.002 62 mol) in dichloromethane (200 ml). The mixture was stirred overnight, washed with water, dried ($MgSO_4$), and evaporated to leave the *amido-β-lactam* (41), which was crystallized from n-hexane–methylene chloride; yield 0.9 g (70%), m.p. 188—190°; $\nu_{max.}$ (Nujol) 3 325 (amide NH), 1 745 (β-lactam CO), 1 735 (ester CO), and 1 678 cm^{-1} (amide CO); δ($CDCl_3$) 2.0—3.18 (2 H, m), 3.32 (2 H, s), 3.82 (3 H, s), 3.86 (3 H, s), 4.07 (3 H, s), 4.36 (1 H, t, *J* 6 Hz), 5.5 (1 H, d), 6.1 (1 H, d), and 6.55—7.87 (12 H, m) (Found: N, 6.05. $C_{29}H_{28}N_2O_6$ requires N, 5.6%).

Compounds (20)—(22), (32), and (33) were obtained similarly (Table 3).

9a-(p-*Aminophenyl*)-1,4,5,9b-*tetrahydro*-1-*methoxy*-2H-*azeto*[2,1-a]*isoquinolin*-2-*one* (16).—Platinum oxide (0.4 g) was added to a solution of the nitro-β-lactam (11) (3 g) in ethyl acetate, and the mixture was hydrogenated at 40 lb in^{-2} overnight. Filtration and evaporation gave the amino-β-lactam (16), m.p. 190—192° (from dichloromethane–n-hexane).

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* The 3 protons of the dihydropyridine ring of (37) gave a deceptively simple ABX type pattern; *J* actually represents ½ (J_{AX} + J_{BX}).