Heterocyclic Compounds. X. Bis(2-chloroethyl)amino Substituted β-Lactams as Potential Antineoplastic Agents (1)

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The synthesis of variously substituted β-lactams carrying a bis(2-chloroethyl)amino group is described. Some of these compounds show mild antitumor activity and low toxicity.

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The administration of anticancer chemotherapeutic agents results in lowering of immunological responses of the patients and often exposes them to severe infection. β-Lactam antiboitics are given simultaneously with the mustards to reduce the chances of uncontrolled infection. The object of this investigation is to synthesize and biologically evaluate compounds in which both the moieties, that is, an alkylating group and a β-lactam ring structure are incorporated. The use of such compounds could serve the function of an anticancer agent with reduced toxicity.

In an attempt to prepare such penicillin-based nitrogen mustards we have synthesized several β-lactam based alkylating agents and their activity against Ehrlich solid carcinoma in the mouse is reported.

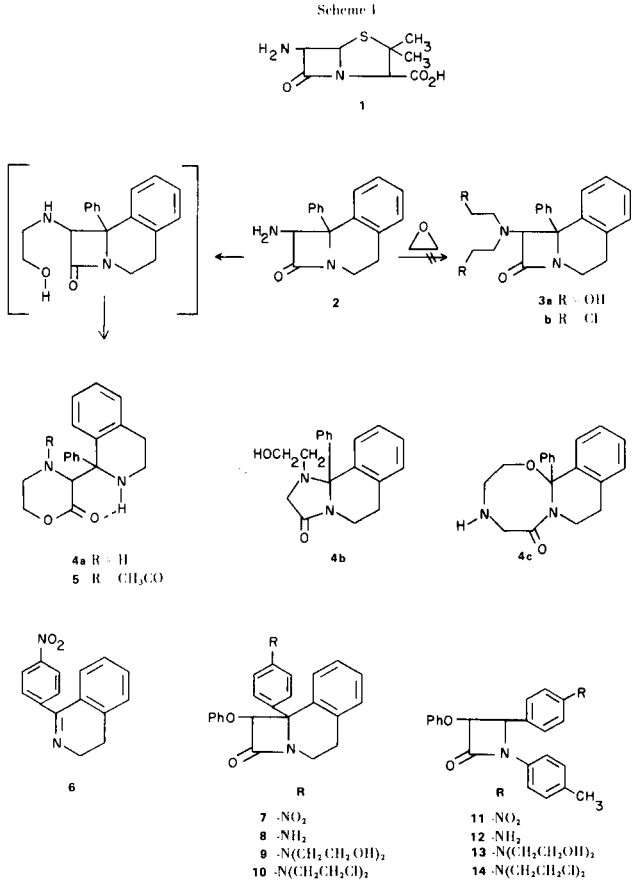
The α-amino-β-lactam (**2**) (2) which is structurally analogous to 6-aminopenicillanic acid (**1**) was chosen as the model compound in which the amino function could be transformed into a nitrogen mustard (**3b**) by known chemical reactions (3).

$$-NH_2 \rightarrow -N(CH_2CH_2OH)_2 \rightarrow -N(CH_2CH_2Cl)_2$$

However, when **2** was treated with ethylene oxide under acidic conditions the product did not show the spectral characteristics of a bis-2-hydroxyethylamino-β-lactam. It was found that the β-lactam ring of **2** was completely cleaved under these mild conditions. Analysis of the infrared spectrum of the product revealed the presence of a lactone ring and an imino group but the absence of hydroxy groups. Of the various structures, such as **4a**, **4b** or **4c** that can be assigned to this rearrangement product, the nmr and mass spectral data correspond to structure **4a**. Reaction of **4a** with acetyl chloride even under refluxing conditions gave only a monoacetate which can best be represented by structure **5**. The other N-H in **4a** appears to be strongly hydrogen bonded to the lactone carbonyl. These structural changes are delineated in Scheme I. It may be pointed out that isolated instances of β-lactam ring cleavage through the participation of nucleophiles present in C_3 substituents and suitably located in relation to the amide bond have been reported earlier by previous workers (4,5).

Attempts were made next to incorporate the bis(2-chloroethyl)amino group at other locations of the β-lactam molecule. The tricyclic β-lactam (**7**) was prepared by the reaction of phenoxyacetyl chloride and 1-(*p*-nitrophenyl)-3,4-dihydroisoquinoline (**6**) (2) in the presence of triethylamine. Catalytic reduction of the nitro group to the amino function and subsequent reaction with ethylene oxide followed by treatment with thionyl chloride afforded **10**. The monocyclic β-lactam (**11**) was converted to **14** using a similar sequence of reactions.

Scheme I



The synthesis of compounds **10** and **14** revealed that the β-lactam ring is compatible with reagents and reaction conditions necessary to generate nitrogen mustards pro-

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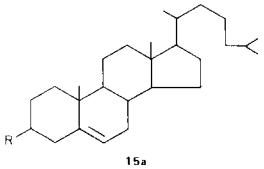
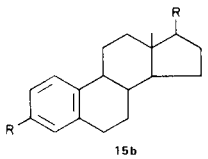
vided the amino group involved is sufficiently removed from the β-lactam amide carbonyl. It was, therefore, considered desirable to incorporate the phenestrin (**15a**) (6) or "estradiol mustard" (**15b**) (10) side chain on the α-carbon atom of these heterocycles. This would also eliminate the close proximity of the interfering group. The incorporation of this group in these heterocycles was contingent upon an easy access to α-hydroxy-β-lactams.

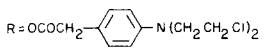
Condensation of *p*-methoxybenzylidene-*p*-toluidine (**16**) with *t*-butoxyacetic acid in the presence of diethoxyphosphochloridate and triethylamine (7) resulted in the α-*t*-butoxy-β-lactam (**18**) (8). This β-lactam could be converted to the corresponding α-hydroxy-β-lactam (**19**) (8) in poor yield by refluxing with trifluoroacetic acid. An extensive cleavage of the β-lactam ring occurred during the generation of the hydroxy function. Alternatively, the α-benzyloxy-β-lactam (**17**) (8) was prepared by the reaction of **16** with benzyloxyacetyl chloride in the presence of triethylamine. Hydrogenolysis of **17** resulted in the hydroxy-β-lactam (**19**) (8). This method of generation of the α-hydroxy-β-lactams was found to be erratic. The purity of the benzyloxy-β-lactam was critical for the success of the hydrogenolysis reaction.

We have now developed a facile method for generating α-hydroxy-β-lactams. In this method the ether linkage in **17** could be cleaved in very good yield with boron trichloride (**9a**) or boron tribromide (**9b**) at 0° without damage to the β-lactam ring. The benzyloxy and *t*-butoxy groups could be cleaved in about 1.5 hours, whereas methoxy and phenoxy groups required a much longer (~ 8-10 hours) reaction time. We have found this to be the method of choice as it can be operated under mild conditions, provides selectivity and gives good yields of α-hydroxy-β-lactams.

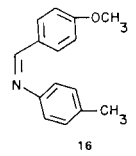
The reaction of **19** with *p*-nitrophenylacetyl chloride gave the nitroester (**20**) which was catalytically reduced to the amino derivative (**21**) and subsequently acylated to **22** with phenoxyacetyl chloride. The conversion of **21** to **24** via **23** was uneventful.

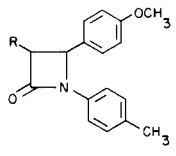






Using a similar reaction sequence the substituted β-lactam (**33**) was prepared from 1-phenyl-3,4-dihydroisoquinoline (**25**).





R

17 OCH_2Ph

18 O-t-C_4H_9

19 OH

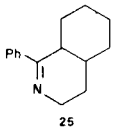
20 $OCOCH_2$–NO_2

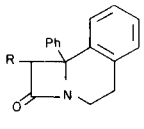
21 $OCOCH_2$–NH_2

22 $OCOCH_2$–$NHCOCH_2OPh$

23 $OCOCH_2$–$N(CH_2CH_2OH)$

24 $OCOCH_2$–$N(CH_2CH_2Cl)_2$





R

26 OCH_2Ph

27 O-t-C_4H_9

28 OH

29 $OCOCH_2OPh$

30 $OCOCH_2$–NO_2

31 $OCOCH_2$–NH_2

32 $OCOCH_2$–$N(CH_2CH_2OH)_2$

33 $OCOCH_2$–$N(CH_2CH_2Cl)_2$

Biological Activity.

The compounds **33**, **24**, **14** and **10** were tested against Ehrlich solid carcinoma in mice. Mechlorethamine was also tested simultaneously as a standard alkylating agent.

Ehrlich carcinoma was induced in 18 to 20 g. CD_1 mice by the subcutaneous (ventrolateral) injection of 0.5 ml. of a 1-10 saline-diluted ascitic tumor cell suspension. Test substances were dissolved in water (mechlorethamine) or suspended in 0.1% carboxymethyl cellulose (**10**, **14**, **24**, **33**) and mice received 1.0 ml. intraperitoneally of the test substances or water beginning immediately after implantation and daily thereafter for a total of 8 treatments.

Table 1

Effect of β-Lactam Nitrogen Mustards

Compound	Dose mg./kg. ip x 8	Number of Survivors/ Number Tested	C/T Index	% Inhibition of Tumor Growth (a)
Mechlorethamine	1.0	2/8	5.8	83
	0.5	14/16	2.4	59
	0.25	15/16	1.5	33
33	100	7/16	12.9	92
	50	16/16	4.2	76
	25	20/24	2.1	52
	12.5	8/8	0.8	-25
24	100	8/8	1.1	-10
14	100	7/8	1.9	47
10	100	8/8	1.1	10

(a) % Inhibition of tumor growth = $100(1-\frac{1}{\frac{C}{T}})$.

Mice were sacrificed one day after the last treatment, tumors were excised, and the average weight of tumors from water-treated animals (C) compared to the average weight of tumors from drug-treated animals (T). A C/T index of 2.0 or more indicated ≥ 50% inhibition of tumor growth and an antitumor effect.

The effects of mechlorethamine, and the compounds under examination against Ehrlich solid carcinoma tumor in mice are shown in Table 1.

From the results shown in Table 1 it can be seen that mechlorethamine was active at a dose of 1.0 mg./kg. (intraperitoneally) but only 2 of 8 treated mice survived at this dose. Mechlorethamine was active at 0.5 mg./kg. and inactive at 0.25 mg./kg. Compound **33** was active at 100 mg./kg. but only 7 of 16 treated mice survived. Compound **33** was active at doses of 50 and 25 mg./kg. and inactive at 12.5 mg./kg. Compounds **10**, **14** and **24** were without antitumor effect at the dose tested (100 mg./kg.).

The LD_{50} of the β-lactam mustard (**33**), 72 hours after a single intraperitoneal injection, was found to be greater than 500 mg./kg.

EXPERIMENTAL

Ir spectra were recorded with a Perkin-Elmer Infracord. Nmr spectra were recorded with a Varian A60A spectrometer using deuterated chloroform or DMSO-d_6 and mass spectra were obtained with a Perkin-Elmer RMU-7 Mass Spectrometer. Microanalyses were performed by A. Bernhardt, Mikroanalytisches Laboratorium im Max-Planck Institut, Mulheim (Ruhr), West Germany.

cis-1-(*p*-Tolyl)-3-benzyloxy-4-(*p*-anisyl)azetidin-2-one (**17**).

A solution of the Schiff base (**16**, 5.0 g., 0.02 mole) and triethylamine (2.5 g., .025 mole) in methylene chloride (200 ml.) was stirred at room temperature while a solution of benzyloxyacetyl chloride (4.6 g., 0.02 mole) in methylene chloride (150 ml.) was added dropwise over a period of 2 hours. The contents were stirred at room temperature for an additional 12 hours. The reaction mixture was then washed with water, dried (magnesium sulfate) and the solvent removed under reduced pressure. The residue was chromatographed over Florisil with methylene chloride as eluant. Recrystallization from methylene chloride-hexane gave 4.2 g. (56%) of **17**, m.p. 159-160 (8).

By using the same general method, the β-lactams **7**, **11**, and **26** were synthesized from the appropriate acid chlorides and Schiff bases or cyclic imines.

The β-lactams **17**, **18** and **27** were synthesized by using diethyl phosphochloridate and an α-substituted acetic acid in presence of triethylamine following a method described earlier (7).

Synthesis of α-Hydroxy-β-lactams.

cis-1-(*p*-Tolyl)-3-hydroxy-4-(*p*-anisyl)azetidin-2-one (**19**).

a.

A solution of **18** (1.0 g.) in 5 ml. trifluoroacetic acid (TFA) was refluxed for 20 minutes. The TFA was removed by distillation at 50° under reduced pressure. The residue was dissolved in methylene chloride, washed with 5% sodium bicarbonate solution, water and dried (magnesium sulfate). The solvent was removed and the residue was crystallized from methylene chloride-hexane, affording **19**, 0.3 g. (40%), m.p. 136-137° (8).

b.

A solution of the β-lactam (**17**, 1.1 g.) in 125 ml. of THF was hydrogenated in the presence of palladium on carbon (0.4 g.) under a pressure of 50 psi for 12 hours. Removal of the catalyst, followed by evaporation of the solvent under reduced pressure, gave **19** (0.76 g., 90%).

c.

To a stirred solution of 3.3 g. of benzyloxy-β-lactam (**17**) in 100 ml. methylene chloride was added dropwise over a period of 0.5 hour, a solution of boron tribromide (2.5 g.) in 50 ml. methylene chloride at 0° under anhydrous conditions. Stirring was continued for an additional 1 hour. The course of the reaction was followed by periodic examination of the infrared spectra

Table 2

Analytical and Spectral Data

Compound No.	M.p. °C	Yield %	Formula	Analysis (a) C	H	N	Spectral Data
4a	204-206	60	$C_{19}H_{20}N_2O_2$	73.82 (74.00)	6.62 (6.54)	8.96 (9.08)	ir. (nujol): 3350, 1680 cm^{-1}; nmr (deuteriochloroform): δ 2.5-3.0 (m, 4H), 3.3-4.0 (m, 4H), 4.2-4.5 (m, 3H), 7.2-7.5 (b, 9H); M^+ at m/e 308
5	222	95	$C_{21}H_{22}N_2O_3$	72.16 (71.98)	6.43 (6.33)	8.06 (7.99)	ir (nujol): 1700, 1680 cm^{-1}; nmr (deuteriochloroform): δ 2.1 (s, 3H), 2.2-4.4 (m, 10H), 7.0-7.5 (b, 9H); M^+ at m/e 350
7	192-195	65	$C_{23}H_{18}N_2O_4$				ir (nujol): 1730 cm^{-1}; nmr (deuteriochloroform): δ 2.75 (m, 2H), 3.8 (m, 2H), 5.3 (s, 1H), 6.9-8.1 (m, 13H)
8	185-187	85	$C_{23}H_{20}N_2O_2$				ir (nujol): 3400, 1750 cm^{-1}; nmr (deuteriochloroform): δ 2.7 (m, 2H), 2.9 (b, 2H), 3.7 (m, 2H), 5.5 (s, 1H), 6.6-7.9 (b, 13H); M^+ at m/e 356
9	160-162	75	$C_{27}H_{28}N_2O_4$	72.65 (72.95)	6.56 (6.35)	6.22 (6.30)	ir (nujol): 3330, 1740 cm^{-1}; nmr (deuteriochloroform): δ 2.7 (m, 2H), 3.1-3.7 (b, 12H), 5.45(s, 1H), 6.6-7.5 (m, 13H)
10	165-167	70	$C_{27}H_{26}Cl_2N_2O_2$	67.81 (67.36)	5.72 (5.41)	5.09 (5.82)	ir (nujol) 1740 cm^{-1}; nmr: δ 2.7 (m, 2H), 3.4-3.8 (b, 10H), 5.5 (s, 1H), 6.6-7.5 (m, 13H)
11	164-166	70	$C_{22}H_{18}N_2O_4$				ir (nujol): 1750 cm^{-1}; nmr (deuteriochloroform): δ 2.2 (s, 3H), 5.01 (d, 1H, J = 8 Hz), 5.5 (d, 1H, J = 6 Hz), 6.6-7.6 (b, 13H)
12	182-185	85	$C_{22}H_{20}N_2O_2$	76.54 (76.72)	5.93 (5.85)	8.14 (8.13)	ir (nujol): 3400, 1760 cm^{-1}; nmr (deuteriochloroform): δ 2.25 (s, 3H), 2.9 (b, 2H), 5.1 (d, 1H, J = 6 Hz), 5.5 (d, 1H, J = 6 Hz), 6.5-7.5 (b, 13H)
13	95-97	60	$C_{26}H_{28}N_2O_4$	71.96 (72.20)	6.80 (6.53)	6.38 (6.48)	ir (nujol): 3300, 1740 cm^{-1}; nmr δ 2.25 (s, 3H), 3.0-3.8 (b, 10H), 5.15 (d, 1H, J = 6 Hz) 5.45 (d, 1H, J = 6 Hz), 6.5-7.4 (b, 13H)
14	145-147	65	$C_{26}H_{26}Cl_2N_2O_2$	66.45 (66.52)	6.00 (5.58)	5.71 (5.97)	ir (nujol): 1730 cm^{-1}; nmr (deuteriochloroform): δ 2.28 (s, 3H), 3.6 (s, 8H), 5.25 (d, 1H, J = 6 Hz), 5.5 (d, 1H, J = 6 Hz), 6.5-7.5 (b, 13H)
20	142-145	70	$C_{25}H_{22}N_2O_6$				ir (nujol): 1750, 1740 cm^{-1}; nmr (deuteriochloroform): δ 2.32 (s, 3H), 3.52 (s, 2H), 3.85 (s, 3H), 5.42 (d, 1H, J = 6 Hz), 6.05 (d, 1H, J = 6 Hz), 6.85 (d, 2H, J = 8 Hz), 7.1-7.5 (m, 8H), 8.2 (d, 2H, J = 8 Hz); M^+ at m/e 446
21	160-162	65	$C_{25}H_{24}N_2O_4$				ir (nujol): 3350, 1760 and 1740 cm^{-1}; nmr (deuteriochloroform: δ 2.32 (s, 3H), 2.8 (b, 2H), 3.3 (q, 2H), 3.82 (s, 3H), 5.35 (d, 1H, J = 6 Hz), 5.85 (d, 1H, J = 6 Hz), 6.5-7.4 (m, 12H)
22	163-165	80	$C_{33}H_{30}N_2O_6$	71.80 (71.79)	5.50 (5.49)	4.77 (5.09)	ir (nujol): 3350, 1760 and 1740 cm^{-1}; nmr (deuteriochloroform): δ 2.3 (s, 3H), 3.4 (q, 2H), 3.7 (s, 3H), 4.75 (s, 2H), 5.35 (d, 1H, J = 6 Hz), 5.85 (d, 1H, J = 6 Hz), 6.5-7.6 (m, 17H), 8.3 (b, 1H)

Table 2 Continued

Compound No.	M.p. °C	Yield %	Formula	Analysis (a) C	H	N	Spectral Data
23	91-93	70	$C_{29}H_{32}N_2O_6$	69.00 (69.03)	6.39 (6.39)	5.49 (5.55)	ir (nujol): 3330, 1760 and 1840 cm^{-1}; nmr (deuteriochloroform): δ 2.3 (s, 3H), 3.1-3.8 (b, 15H), 5.3 (d, 1H, J = 6 Hz), 5.82 (d, 1H, J = 6 Hz), 6.6-7.4 (m, 12H); M^+ at m/e 504
24	148-149	60	$C_{29}H_{30}Cl_2N_2O_4$	64.12 (64.32)	5.56 (5.54)	5.14 (5.17)	ir (nujol): 1740 cm^{-1}; nmr (deuteriochloroform): δ 2.3 (s, 3H), 3.3 (m, 2H), 3.7 (s, 8H), 3.82 (s, 3H), 5.3 (d, 1H, J = 6 Hz), 5.9 (3, 1H, J = 6 Hz), 6.6-7.4 (m, 12H); M^+ at m/e 540
26	132-134	75	$C_{24}H_{21}NO_2$	81.02 (81.10)	5.88 (5.96)	3.96 (3.94)	ir (nujol): 1740 cm^{-1}; nmr (deuteriochloroform): δ 2.7 (m, 2H), 3.7 m (2H), 4.4 (s, 2H), 4.9 (s, 1H), 7.5 (m, 14H)
27	129-130	60	$C_{21}H_{23}NO_2$				ir (nujol): 1730 cm^{-1}; nmr (deuteriochloroform): δ 1.3 (s, 9H), 2.65 (m, 2H), 3.7 (m, 2H), 5.2 (s, 1H), 7.2-7.5 (b, 9H); M^+ at m/e 321
28	235-237	75	$C_{17}H_{15}NO_2$	77.09 76.96	5.68 5.70	5.42 5.28	ir (nujol): 3350, 1720 cm^{-1}; nmr (deuteriochloroform): δ 2.7 (m, 2H), 3.6 (m, 2H), 4.95 (s, 1H), 5.25 (b, 1H), 7.2-7.5 (b, 9H)
29	162-165	80	$C_{25}H_{21}NO_4$	75.25 (75.19)	5.33 (5.26)	3.61 (3.51)	ir (nujol): 1740 cm^{-1}; nmr (deuteriochloroform): δ 2.8 (m, 2H), 3.8 (m, 2H), 4.3 (q, 2H, J = 18 Hz), 5.95 (s, 1H), 6.6-8.0 (b, 14H)
30	206-208	75	$C_{25}H_{20}N_2O_5$				ir (nujol): 1750, 1680 and 1600 cm^{-1}; nmr (deuteriochloroform): δ 2.7 (m, 2H), 3.42 (q, 2H, J = 18 Hz), 3.75 (m, 2H), 5.85 (s, 1H), 7.05 (s, 2H, J = 8 Hz), 7.1-7.5 (b, 9H), 8.1 (d, 2H, J = Hz); M^+ at m/e 428
31	130-133	80	$C_{25}H_{22}N_2O_3$				ir (nujol): 3350, 1750 and 1740 cm^{-1}; nmr (deuteriochloroform): δ 2.7 (m, 2H), 2.8-3.8 (m, 6H), 5.8 (s, 1H), 6.5-7.5 (m, 13H); M^+ at m/e 398
32	123-125	70	$C_{29}H_{30}N_2O_5$				ir (nujol): 3300, 1720 cm^{-1}; nmr (deuteriochloroform): δ 2.7 (m, 2H), 3.1-3.8 (m, 14H), 5.75 (s, 1H), 7.1 (d, 2H, J = 8 Hz), 7.2-7.5 (b, 9H), 8.1 (d, 2H, J = 8 Hz); M^+ at m/e 486
33	107-108	65	$C_{29}H_{28}Cl_2N_2O_3$	66.86 (66.54)	5.54 (5.35)	5.16 (5.35)	ir (nujol): 1730, 1740 cm^{-1}; nmr (deuteriochloroform): δ 2.8 (m, 2H), 3.2 (m, 2H), 3.65 (s, 8H), 5.8 (s, 1H), 8.6 (q, 4H, J = 8 Hz), 7.2-7.5 (b, 9H)

(a) Values in parentheses refer to calculated percentages.

of the reaction contents. The disappearance of the ether β-lactam carbonyl at 1740-1760 cm^{-1} and appearance of the hydroxy-β-lactam carbonyl at 1700-1720 cm^{-1} was indicative of the completion of this reaction. Ice-cold water (200 ml.) was then added. After neutralizing the contents with 5% sodium bicarbonate solution the organic layer was separated. The aqueous layer was extracted with methylene chloride. The combined methylene chloride phase was dried (magnesium sulfate) and the solvent removed under reduced pressure. The residue was recrystallized from methylene chloride-hexane, m.p. 136-137° (8) (2.3 g., 80%).

In a similar manner, the β-lactams **18**, **26** and **27** were converted to the corresponding hydroxy-β-lactams **19** and **28**.

cis-1-(*p*-Tolyl)-3-(*p*-Nitrophenylacetate)-4-(*p*-anisyl)azetidin-2-one (**20**).

p-Nitrophenylacetyl chloride (2.2 g., 0.011 mole) in dry methylene chloride (50 ml.) was added dropwise to a stirred solution of the α-hydroxy-β-lactam (**19**, 2.8 g., .01 mole), triethylamine (1.5 g., .015 mole) in methylene chloride (100 ml.). After stirring overnight at room temperature the reaction contents were washed with water, dried (magnesium sulfate), and the solvent removed under reduced pressure. The residue was chromatographed over Florisil with methylene chloride as eluant. Recrystallization from methylene chloride-hexane gave 3.1 g. (70%) of **20**, m.p. 143-145°.

The compounds **22**, **29** and **30** were also prepared by treating the corresponding β-lactams with appropriate acid chlorides in the presence of a base.

Synthesis of Amino-β-lactams.

Platinum oxide (0.5 g.) was added to a solution of 5 g. of the nitro-β-lactam (**7**) in THF and the mixture hydrogenated at 40 psi overnight, filtered and evaporated to give **8** (4.1 g.), m.p. 185-187°.

In a similar manner, the nitro-β-lactams **11**, **20** and **30** were converted to the corresponding amino derivatives.

General Method for the Synthesis of Bis(2-chloroethyl)amino-β-lactams.

a.

To a stirred solution of 72 ml. of 80% acetic acid and 2.6 g. of 1-(*p*-tolyl)-4-*p*-anisylazetidin-2-one 3-*p*-aminophenylacetate (**21**) at 0° were gradually added 16 ml. of cooled ethylene oxide. The stirring was continued for an additional 3 hours. The reaction contents were then set aside overngiht, then neutralized with 20% sodium bicarbonate solution, extracted with methylene chloride (100 x 4 ml.) and dried (magnesium sulfate). The solvent was removed under reduced pressure and the residue recrystallized from methylene chloride-hexane to afford **23**, m.p. 91-93°.

The bis-hydroxy-β-lactams **9**, **13** and **32** were similarly obtained from **8**, **12** and **31** respectively.

The reaction of the α-amino-β-lactam (**2**) with ethylene oxide under similar conditions afforded **4** in 60% yield, m.p. 204-206° (methylene chloride-hexane).

b.

To a solution of bis-hydroxy-β-lactam (**23**, 5.0 g., 0.01 mole) in 150 ml. of methylene chloride under nitrogen atmosphere was added dropwise thionyl chloride (2.4 g., 0.02 mole) in methylene chloride (50 ml.). The reaction mixture was stirred overnight at room temperature, washed with water, dried (magnesium sulfate) and the solvent removed under reduced pressure. The residue was chromatographed over Florisil with methylene chloride as eluant. Recrystallization from methylene chloride-hexane gave **24**, m.p. 142-143°.

The dichloro-β-lactams **10**, **14** and **33** were obtained in a similar manner from **9**, **13** and **32** respectively.

Acetylation of **4**.

To a solution of **4** (0.6 g., 0.002 mole) in 150 ml. methylene chloride containing acetyl chloride (0.24 g., 0.003 mole) were added dropwise with stirring 0.3 g. (0.003 mole) of triethylamine. The mixture was refluxed for 4 hours. After cooling, the reaction mixture was washed with 5% sodium bicarbonate solution, water and dried (magnesium sulfate). The solvent was removed and the residue was recrystallized from methylene chloride-hexane, m.p. 220° (95%).

The analytical and spectral data on all of these compounds are given in Table 2.

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