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A convenient synthesis of α-hydroxy-β-lactams has been devised that involves the annelation of an imine with benzyloxyacetyl chloride and triethylamine and subsequent hydrogenolysis in the presence of palladium on carbon. In most cases a *cis*-β-lactam was obtained. A thioimidate can also be used as the imino component in the annelation reaction but the hydrogenolysis step fails. The annelation of the appropriate thiazoline to a 6-*epi*-penicillin derivative occurred much more readily with benzyloxyacetyl chloride than with azidoacetyl chloride.

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Methoxycephalosporins produced by streptomyces (2) and their synthetic analogs (3) and the 6-methoxypencillins (4) show enhanced antibiotic activity against Gram-negative organisms. This finding has attracted attention to the synthesis of α-hydroxy-β-lactams. Until recently only a few members of this class had been reported (5a,b). Henery-Logan and Rodericks (6) had obtained a 3-hydroxy-2-azetidinone as a byproduct in the course of diazotization of 3-amino-2-azetidinones.

The first synthesis of 6-hydroxypenam was reported by Hauser and his co-workers (5c). Since then Sheehan and co-workers (5d) have also reported a synthesis of such compounds starting from 6-aminopenicillanic acid. Bose, *et al.*, (7) have recently described a synthesis of α-hydroxy-β-lactams in which the hydroxy group is tertiary in character. We wish to report a convenient synthesis of α-hydroxy-β-lactams. Our method consists in the reaction of a Schiff-base with a substituted acetyl chloride in the presence of triethylamine (TEA). The substituent at C-3 is subsequently converted into a hydroxy group.

Thus, when the Schiff-base **3** derived from *p*-toluidine and *p*-anisaldehyde was treated with benzyloxyacetyl chloride in presence of TEA at room temperature, the β-lactam **12** was formed in high yield. The nmr of the crude reaction product revealed the formation of only one of the two possible isomers. The coupling constant of C-3 and C-4 protons was of the order of 6 Hz, which is indicative of their *cis* disposition (8). The benzyloxy group situated at C-3 was smoothly transformed into the hydroxy function by hydrogenolysis in the presence of 10% palladium on carbon at 42 psi in a Parr hydrogenator. The presence of the hydroxyl function in **13** was demonstrated by its conversion to the corresponding methoxy derivative **14** on treatment with silver oxide/methyl iodide. The *cis* configuration of the α-hydroxy-β-lactam was retained during its conversion to the methoxy derivative. The reaction of **13** with phenoxyacetyl chloride, phenylacetyl chloride and triflouroethyl sulphonyl chloride gave the esters **15**, **16** and **17**, respectively.

Recently it has been shown (9) that a secondary hydroxy group can be replaced with a phthalimido group by reaction with phthalimide, triphenylphosphine and diethyl azodicarboxylate. This substitution proceeds with inversion. The phthalimido group can be converted to an amino group by hydrazinolysis. In the hope of devising a convenient synthesis of α-amino-β-lactams, **13** was treated with phthalimide, triphenylphosphine and diethyl azodicarboxylate at room temperature but no reaction occured: probably because of steric hindrance. This type of reaction is known to be sensitive to the steric environment.

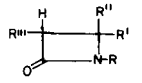
Using the method described earlier for the synthesis of β-lactams and employing the appropriate Schiff-bases, the benzyloxy-β-lactams **18** and **19** were also synthesized in 60-70% yield. Nmr spectroscopy of these β-lactams also showed the *cis* relationship of the C-3 and C-4 protons. With a view to introducing a free COOH group in the β-lactam, *p*-carboxybenzaldehyde was silylated with trimethylsilyl chloride and then treated with *p*-toluidine (10). The Schiff-base **6** (*p*-carboxybenzylidene-*p*-toluidine) obtained after the work up was again silylated and treated with benzyloxyacetyl chloride in presence of TEA to give the β-lactam **20** with a free carboxy group on the phenyl ring at C-4. The β-lactam **20** obtained in this reaction was exclusively *cis* in configuration.

The reaction of methyl *N*-phenylbenzothioimidate **4** gave the β-lactam **21** as a single isomer. No attempt was made to rigorously establish the stereochemistry of **21**. However by the analogy with the previous work in this laboratory (11) we have assigned the *Z* configuration to **21**.

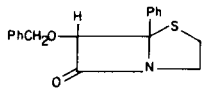
Attempts to cleave the benzyloxy group in **21** *via* hydrogenolysis were unsuccessful. The S-methyl group seems to interfere with this reaction. The conversion of **21** to the sulfoxide β-lactam (**22**) by oxidation with *m*-chloroperoxybenzoic acid took place smoothly. The benzyloxy group in **22** was also resistant to hydrogenolysis even in the presence of large amounts of 10% palladium on carbon catalyst.

The reaction of benzylidineaniline (**1**) with benzyloxyacetyl chloride in presence of TEA, resulted in β-lactam **23**. The nmr spectrum of the crude reaction product revealed the presence of *cis* and *trans* isomers (40:60 ratio). The benzyloxy group of **23** was smoothly converted to the hydroxy function upon hydrogenation resulting in β-lactam **24**. The reaction of **7** with benzyloxyacetyl chloride, however, resulted exclusively in the formation of the *trans* β-lactam **25**.

In this general reaction, it appears that the stereochemistry of the product cannot be predicted unequivocally.



12. R = $pCH_3C_6H_4$, R' = $pCH_3OC_6H_4$, R'' = H, R''' = OCH_2Ph (*cis*)
13. R = $pCH_3C_6H_4$, R' = $pCH_3OC_6H_4$, R'' = H, R''' = OH (*cis*)
14. R = $pCH_3C_6H_4$, R' = $pCH_3OC_6H_4$, R'' = H, R''' = OCH_3 (*cis*)
15. R = $pCH_3C_6H_4$, R' = $pCH_3OC_6H_4$, R'' = H, R''' = $OCOCH_2OPH$ (*cis*)
16. R = $pCH_3C_6H_4$, R' = $pCH_3OC_6H_4$, R'' = H, R''' = $OCOCH_2PH$ (*cis*)
17. R = $pCH_3C_6H_4$, R' = $pCH_3OC_6H_4$, R'' = H, R''' = $OSO_2CH_2CF_3$ (*cis*)
18. R = $pCH_3C_6H_4$, R' =  , R'' = H, R''' = OCH_2Ph (*cis*)
19. R = $pCH_3C_6H_4$, R' = $oNO_2C_6H_4$, R'' = H, R''' = OCH_2Ph (*cis*)
20. R = $pCH_3C_6H_4$, R' = $pHO_2CC_6H_4$, R'' = H, R''' = OCH_2Ph (*cis*)
21. R = R' = Ph, R'' = SCH_3, R''' = OCH_2Ph
22. R = R' = Ph, R'' = $SOCH_3$, R''' = OCH_2Ph
23. R = R' = Ph, R'' = H, R''' = OCH_2Ph (*cis & trans*)
24. R = R' = Ph, R'' = H, R''' = OH (*cis & trans*)
25. R = α-$C_{10}H_7$, R' = Ph, R'' = H, R''' = OCH_2Ph (*trans*)



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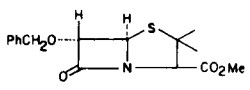

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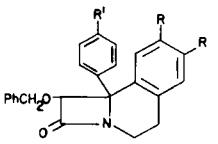

28. R = R = OCH_3, R' = Br
29. R = R = H, R' = NH_2
30. R = R = H, R' = NH_2

Apparently the configuration of the β-lactam depends upon several factors, including the structure of the Schiff-base and the nature of the acid chloride (12,13).

This synthesis of 3-benzyloxyazetidine-2-one has been extended to α-benzyloxy polycyclic β-lactams. Thus, 2-phenyl-2-thiazoline **8** on treatment with benzyloxyacetyl chloride afforded the penam **26** in 60% yield. When 4,4-dimethyl-5-carbomethoxy-2-thiazoline **9** was similarly treated with benzyloxyacetyl chloride, the penam **27** was formed in 30% yield. It may be noted that using a similar sequence of reactions the corresponding 6-azido and 6-methoxy penams were obtained in 5-10% yield. The stereochemistry of the penam **27** was ascertained to be *trans* on the basis of its pmr spectrum.

The cyclic imines **10** and **11** were similarly converted to the tricyclic β-lactams **28** and **29** on treatment with benzyloxacetyl chloride. The hydrogenation of **29** by using 10% palladium on carbon and H_2 under 42 psi pressure reduced only the nitro-group to the amino group to afford the β-lactam **30** the benzyloxy group was unaffected in this reaction. Repeated attempts to cleave the benzyloxy group in **29** were unsuccessful.

EXPERIMENTAL

The ir spectra were recorded on a Perkin-Elmer infracord spectrophotometer calibrated with polystyrene film at 1603 cm^{-1}. The pmr spectra were obtained on a Varian A-60A spectrometer operating at 60 MHz using TMS as an internal standard. The mass spectra were measured on a Hitachi Perkin-Elmer RMU-7 mass spectrometer at 70 eV using an all glass heated inlet system. Thin layer chromatography (tlc) was performed on silica G Plates and spots were developed with iodine vapor or aqueous potassium permanganate solution. Elemental analyses were performed by A. Bernhardt, Max Planck Institute, Mulheim, W. Germany. Melting points were determined in open capillary tubes and are uncorrected.

Benzyloxyacetic Acid.

To a solution of benzyl alcohol (21.6 g., 0.2 mole) in anhydrous benzene (300 ml.) was added sodium hydride (19.2 g., 0.4 mole) and the contents stirred at room temperature for 3 hours. To this solution of monochloroacetic acid (19.9 g., 0.2 mole) in 60 ml. of benzene was then added dropwise and the contents refluxed for 15 hours. The reaction mixture was cooled in an ice-bath and excess sodium hydride was decomposed with water. The aqueous layer was separated, acidified with dilute hydrochloric acid and extracted with dichloromethane (3 x 150 ml.). The organic layer was washed with water, and dried (magnesium sulfate). Evaporation of the solvent under reduced pressure gave 16.9 g. (80%) of the title compound as a colorless oil, ir (nujol): 3226 (b, COOH), 1724 cm^{-1} (O=C-OH); nmr (deuteriochloroform): 4.14 (s, 2H), 4.62 (s, 2H), 7.67 (s, 5H), 10.35 (s, 1H).

Benzyloxyacetyl Chloride.

To a solution of benzyloxyacetic acid (16.6 g., 0.1 mole) in 200 ml. of anhydrous benzene was slowly added 20 ml. of thionyl chloride and refluxed for 1.5 hours. Excess thionyl chloride and benzene were distilled off under reduced pressure. The product 17 g. (92%) was used as such for further reactions, ir (nujol): 1800 cm^{-1} (C=O); nmr (deuteriochloroform): 4.4 (s, 2H), 4.63 (s, 2H), 7.37 (s, 5H).

General Method for the Synthesis of 3-Benzyloxy-β-lactams.

cis-1-(*p*-Tolyl)-3-benzyloxy-4-(*p*-anixyl) azetidin-2-one (**12**).

A solution of the Schiff-base **3** (10 g., 0.04 mole) and TEA (5.1 g., 0.05 mole) in dichloromethane (200 ml.) was stirred at room temperature while a solution of benzyloxyacetyl chloride (9.2 g., 0.05 mole) in dichloromethane (150 ml.) was added dropwise over a period of 2 hours. The mixture was stirred at room temperature for an additional 12 hours. The reaction mixture

Table I

Analytical and Spectral Data

Compound No.	M.p. °C	Yield %	Formula	Analysis (a) C	H	N	Spectral Data
12	162	55	$C_{24}H_{23}NO_3$	76.70 (77.19)	6.20 (6.21)	3.55 (3.75)	Ir 1747 cm^{-1}; nmr δ: 2.25 (s, 3H), 4.74 (s, 3H), 4.31 (s, 2H), 4.89 (d, 1H, J = 5 Hz), 5.08 (d, 1H, J = 5 Hz), 7.0-7.46 (m, 13H).
13	137-138	90	$C_{17}H_{17}NO_3$	71.75 (72.07)	6.20 (6.05)	5.05 (4.95)	Ir 3305, 1705 cm^{-1}; nmr δ: 2.20 (s, 3H), 3.70 (s, 3H), 5.08 (b, 3H), 6.7-7.2 (m, 8H); M^+ at m/e 283.
14	114-115	80	$C_{18}H_{19}NO_3$	73.02 (72.73)	6.85 (6.41)	5.22 (4.71)	Ir 1760 cm^{-1}; nmr δ: 2.15 (s, 3H), 3.2 (s, 3H), 3.85 (s, 3H), 4.75 (d, 1H, J = 5 Hz), 5.15 (d, 1H, J = 5 HZ), 6.85-7.4 (m, 8H).
15	136-137	80	$C_{25}H_{23}NO_5$	72.10 (71.93)	5.63 (5.55)	7.43 (3.36)	Ir 1777, 1740 cm^{-1}; nmr δ: 2.27 (s, 3H), 3.78 (s, 3H), 4.04-4.52 (ABq, 2H, J = 16 Hz), 5.35 (d, 1H, J = 5 Hz), 6.08 (d, 1H, J = 5 Hz), 6.44-7.44 (m, 13H).
16	120-121	85	$C_{25}H_{23}NO_4$	----	----	----	Ir 1780, 1740 cm^{-1}; nmr δ: 2.3 (s, 3H), 3.85 (s, 3H), 4.3 (q, 2H, J = 18 Hz), 5.35 (d, 1H, J = 5 Hz), 6.08 (d, 1H, J = 5 Hz), 7.05-7.5 (b, 13H); M^+ at m/e 401.
17	120-121	85	$C_{19}H_{18}F_3NO_5S$	53.22 (53.14)	4.11 (4.19)	3.19 (3.26)	Ir 1761, 1395 cm^{-1}; nmr δ: 2.30 (s, 3H), 8.80 (s, 3H), 3.64-4.06 (m, 2H), 5.37 (d, 1H, J = 5 Hz), 5.85 (d, 1H, J = 5 Hz), 6.88-7.40 (m, 8H).
18	152-153	70	$C_{21}H_{19}NO_4$	72.42 (72.19)	5.54 (5.48)	4.05 (4.01)	Ir 1765 cm^{-1}; nmr δ: 3.75 (s, 3H), 4.5 (s, 2H), 4.95 (d, 1H), J = 6 Hz), 5.18 (d, 1H, J = 6 Hz), 6.35 (s, 1H), 7.0-7.9 (m, 11H).
19	157-158	65	$C_{23}H_{20}N_2O_4$	71.15 (71.12)	4.90 (5.19)	7.34 (3.47)	Ir 1760 cm^{-1}; nmr δ: 2.25 (s, 3H), 4.52 (s, 2H), 5.1 (d, 1H, J = 6 Hz), 5.82 (d, 1H, J = 6 Hz), 6.95-7.5 (m, 12H), 8.0-8.2 (m, 1H).
20	221-223	60	$C_{24}H_{21}NO_4$	71.60 (71.45)	5.45 (5.25)	3.70 (3.47)	Ir 1740, 1695 cm^{-1}; nmr δ: 3.75 (s, 3H), 4.5 (q, 2H, J = 10 Hz), 5.25 (d, 1H, J = 6 Hz), 5.55 (d, 1H, J = 6 Hz), 7.0-7.6 (m, 13H), 10.5 (b, 1H).
21	153-	70	$C_{23}H_{21}NO_3S$	73.35 (73.58)	5.85 (5.64)	3.78 (3.73)	Ir 1748 cm^{-1}; nmr δ: 2.0 (s, 3H), 4.38 (s, 2H), 5.01 (s, 1H), 7.0-7.4 (m, 15H).
22	185-186	55	$C_{23}H_{21}NO_3S$	69.85 (70.22)	5.66 (5.89)	3.79 (3.56)	Ir: 1750 cm^{-1}; M^+ at m/e 391.
23	148-150	60	$C_{22}H_{19}NO_2$	79.70 (79.47)	5.84 (5.03)	4.41 (4.41)	Ir: 1755 cm^{-1}; nmr (deuteriochloroform): δ 4.8 (m, 4H), 7.1-7.45 (b, 15H); M^+ at m/e 329.
24	118-119	80	$C_{15}H_{13}NO_2$	----	----	----	Ir: 3305, 1705 cm^{-1}; nmr (deuteriochloroform + DMSO) δ: 5.1 (b, 2H), 5.9 (d, 1H, J = 6 Hz), 6.9-7.25 (b, 10); M^+ at m/e 239.
25	122-123	70	$C_{26}H_{21}NO_2$	82.55 (82.29)	5.70 (5.58)	3.76 (3.69)	Ir 1750 cm^{-1}; (q, 2H, J = 13 Hz), 4.25 (d, 1H, J = 2 Hz), 5.2 (d, 1H, J = 2 Hz), 7.1-7.7 (m, 16H), 8.1-8.3 (m, 1H).
26	86- 87	60	$C_{18}H_{17}NO_2S$	69.35 (69.44)	5.53 (5.34)	4.41 (4.50)	Ir 1765 cm^{-1}; nmr δ: 3.2 (m, 2H), 4.2 (m, 2H), 4.25 (s, 2H), 4.92 (s, 1H), 7.0-7.9 (6, 10H).
27	Liq	30	$C_{16}H_{19}NO_4S$	----	----	----	Ir 1760, 1740 cm^{-1}; nmr δ: 1.42 (s, 3H), 1.55 (s, 3H), 3.75 (s, 3H), 4.5 (s, 1H), 4.7 (d, 1H, J = 2 Hz), 5.1 (d, 1H, J = 2 Hz), 4.62 (q, 2H, J = 10 Hz), 7.2 (s, 5H); M^+ at m/e 321.
28	188-189	70	$C_{26}H_{24}BrNO_4$	63.25 (63.15)	5.10 (4.86)	2.72 (2.83)	Ir 1765 cm^{-1}; nmr δ: 2.62 (m, 2H), 3.02 (m, 2H), 3.82 (s, 3H), 3.85 (s, 3H), 4.52 (s, 2H), 4.9 (s, 1H), 6.72 (b, 2H), 7.2-7.35 (m, 9H).
29	124-125	68	$C_{24}H_{20}N_2O_4$	71.45 (71.98)	5.26 (5.03)	7.00 (7.00)	Ir 1760 cm^{-1}; nmr δ: 2.7 (m, 2H), 3.62 (m, 2H), 4.48 (q, 2H), J = 10 Hz), 4.92 (s, 1H), 7.0-7.8 (m, 13H).
30	176-178	80	$C_{24}H_{22}N_2O_2$	----	----	----	Ir 3300, 1750 cm^{-1}; nmr δ: 2.61 (m, 2H), 3.4-3.65 (b, 4H), 4.4 (s, 2H), 4.85 (s, 1H), 6.5 (s, 1H), 6.65 (s, 1H), 7.0-7.3 (m, 11H), M^+ at m/e 370.

(a) Calculated values are in parentheses.

was then washed with water, dried (magnesium sulfate) and the solvent removed under reduced pressure. The residue was chromatographed over Florisil with dichloromethane as eluent. Recrystallization from dichloromethane-hexane gave 8.4 g. (56%) of **12**, m.p. 159-160°.

By using the same general method the β-lactams **18**, **19**, **20**, **21**, **23**, **25**, **26**, **27**, **28** and **29** were synthesized by reacting benzyloxyacetyl chloride with the appropriate Schiff-bases or cyclic imines. The spectral and analytical data on these compounds are given in Table I.

Hydrogenolysis of 3-Benzyloxy-β-lactams.

cis-1-(*p*-Tolyl)-3-hydroxy-4-(*p*-anisyl)azetidin-2-one (**13**).

A solution of the β-lactam **12** (1.1 g., 0.003 mole) in 125 ml. of THF was hydrogenated for 12 hours in the presence of 0.4 g. of 10% palladium on carbon under a pressure of 50 psi. Removal of the catalyst, followed by evaporation of the solvent under reduced pressure afforded **13** (0.76 g., 90% yield), m.p. 137-138° (dichloromethane-hexane).

In a similar manner, the β-lactam **23** was converted to the hydroxy β-lactam **24**.

cis-(1-*p*-Tolyl)-3-methoxy-4-(*p*-anisyl)azetidin-2-one (**14**).

A mixture of α-hydroxy-β-lactam **13** (2.89 g., 0.01 mole), silver oxide (1 g., 0.01 mole), methyl iodide (1.4 g., 0.01 mole) in dry THF was refluxed for 8 hours. The reaction mixture was then filtered and the filtrate evaporated under reduced pressure to give 2.3 g. of **14** (80% yield), m.p. 113-114° (*n*-hexane-dichloromethane).

Acylation of 3-Hydroxy-β-lactams.

cis-(1-*p*-Tolyl)-3-(phenylacetyl)-4-(*p*-anisyl)azetidin-2-one (**16**).

To a solution of the hydroxy-β-lactam **13** (0.56 g., 0.02 mole) in 75 ml. of dichloromethane containing TEA (0.3 g., 0.003 mole) was added phenylacetyl chloride (0.04 g., 0.0025 mole). The reactants were stirred at room temperature for 12 hours, washed with water, dried (magnesium sulfate) and the solvent removed under reduced pressure. The solid residue was recrystallized from dichloromethane-hexane to get **16** (75% yield) m.p. 136-137°.

The 3-acylated-β-lactams **15** and **17** were also prepared by treating **13** with phenoxyacetyl chloride and triflouroethylsulphenyl chloride, respectively.

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