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STUDIES ON LACTAMS—XI[1,2]

SYNTHESIS OF SOME CEPHAM DERIVATIVES

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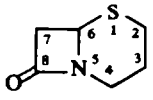
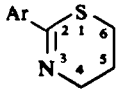
Abstract—A general method has been described for the synthesis of bicyclic α-amido-β-lactams which correspond to the cepham nucleus or its modified forms. The reaction of 2-phenyl-5,6-dihydro-4*H*-1,3-thiazine with azidoacetyl chloride and triethylamine in methylene chloride solution leads to an α-azido-β-lactam which can be hydrogenated in presence of Adam's catalyst to an α-amino-β-lactam and then acylated to give 7-phenoxy-acetamido-6-phenylcepham. A structural variation is obtained by carrying out a similar sequence of reactions starting with 2,2-dimethyl-3-phenyl-5,6-dihydro-1,4-thiazine prepared from aziridine and 2-methyl-2-mercaptopropiophenone. Yet another variant of the cepham nucleus represented by an α-azido-β-lactam, can be synthesized from 2,2,4,6,6-pentamethyl-5,6-dihydro-2*H*-1,3-thiazine.

RECENTLY[3-5] we have described a synthesis of α-azido-β-lactams from azido acid chlorides and imines. The azido group can be reduced and acylated under mild conditions to produce α-amido-β-lactams—structural features which are characteristic of the penicillin and cephalosporin families of antibiotics. We have shown[3] that this approach can lead to a cepham[6] (I) derivative. Now we wish to report the extension of this method to the synthesis of several structural variations of the cepham nucleus.

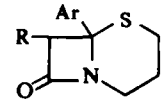
The general sequence of reactions is illustrated by the synthesis of 7-phenoxy-acetamido-6-phenylcepham (VII). The addition of triethylamine under high dilution conditions to a refluxing solution of 2-phenyl-5,6-dihydro-4*H*-1, 3-thiazine (II) and azido acetyl chloride in methylene chloride led to a 23% yield of the azido-β-lactam IV. It was necessary to use Adams catalyst in large amounts for the hydrogenation of IV to the amino-β-lactam VI, the yield in this step was about 55%. Acylation with phenoxyacetyl chloride in presence of triethylamine proceeded in good yield to give the amido-β-lactam VII. All the β-lactams showed the characteristic carbonyl absorption at about 5·70 μ.



I



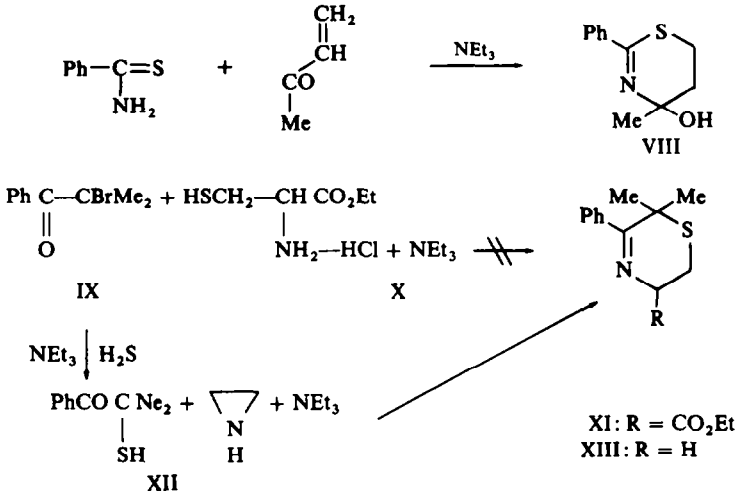
II: Ar = C_6H_5
III: Ar = *p*-NO_2—C_6H_4



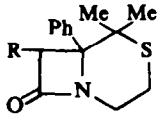
IV: R = N_3, Ar = Ph
V: R = N_3, Ar = *p*-NO_2—C_6H_4
VI: R = NH_2, Ar = Ph
VII: R = Ph OCH_2CONH, Ar = Ph

The condensation of thiobenzamide with methyl vinyl ketone gave the dihydrothiazine derivative VIII.[7] No β-lactam could be isolated from the reaction of VIII

with an excess of azidoacetyl chloride and triethylamine. The condensation of 2-bromo-2-methylpropiophenone (IX) with cysteine ethyl ester hydrochloride (X) was attempted without success to obtain the dihydrothiazine XI which would have provided a cepham with a structural variation. An analogous dihydrothiazine XIII however, was prepared by the reaction of aziridine with 2-mercapto-2-methylpropiophenone (XII). Confirmation of the structure XIII was provided by the NMR spectrum which showed two triplets (J = 5·5 c/s) corresponding to the two adjacent methylene

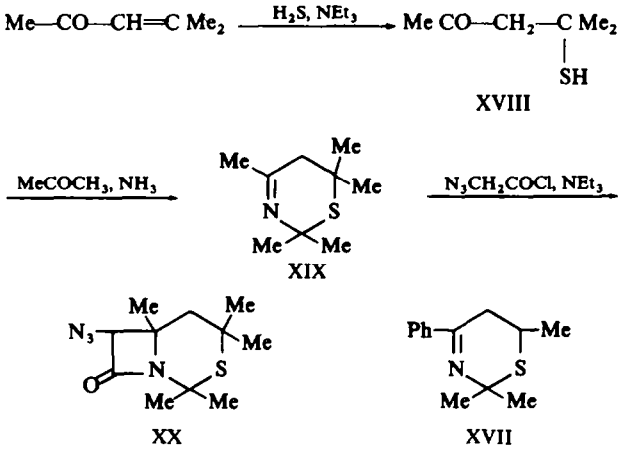


groups coupled to each other. The reaction of XIII with azidoacetyl chloride led to the isolation of *only one* stereoisomeric form of the β-lactam XIV, and the subsequent reduction to XV and acylation proceeded smoothly and the desired amido-β-lactam XVI was obtained.



XIV: R = N_3
XV: R = NH_2
XVI: R = $NHCOCH_2O$ Ph

Yet another variation of cepham (I) was sought in which the S atom would be at position 3 instead of 1. An appropriate imine for it, for example, XVII, could not be obtained when the condensation of acetone was attempted with 2-mercapto-2-methylpropiophenone in presence of ammonia. However, the parallel condensation between 4-mercapto-4-methyl-2-pentanone XVIII, acetone and ammonia afforded the desired 2,2,4,6,6-pentamethyl-5,6-dihydro-2H-1,3-thiazine (XIX).[8] The reaction of XIX with azido acid chloride and triethylamine gave a mixture of products from which an oil was isolated by repeated chromatography which showed infrared bands at 4·78 and 5·71 μ. This material could not be obtained analytically pure but its NMR, and mass spectra indicated it to be essentially the cepham variant XX. Further work in this area is in progress.



EXPERIMENTAL

All mps are uncorrected. NMR spectra were determined on a Varian A-60A instrument using TMS as an internal standard. IR spectra were recorded with a Perkin–Elmer Model 21 spectrometer. The mass spectra were obtained on a CEC 21–103C mass spectrometer equipped with an all-glass, heated inlet system. Microanalysis of the compounds reported were performed by A. Bernhardt at Mikroanalytisches Laboratorium im Max-Planck Institut, Mülheim (Ruhr), West Germany.

2-*Phenyl*-5,6-*dihydro*-4H-1,3-*thiazine* (II) was prepared according to the method described by Lawson and Searle.[9]

7-*Azido*-6-*phenyl cepham* (IV)

To a refluxing soln of II (1·8 g) and azidoacetyl chloride (1·4 g) in 200 ml CH_2Cl_2 was added by the high dilution method 2 ml Et_3N in 75 ml CH_2Cl_2 over a period of 6 hr. The mixture was refluxed for an additional 1½ hr and then stirred overnight at room temp. The solvent was then removed *in vacuo* and the residue extracted with anhydrous ether. The viscous oily residue obtained by the removal of ether was chromatographed over 40 g silica gel column made in benzene. Elution with benzene–CH_2Cl_2 (1:1) afforded an oily residue which solidified on trituration with pet. ether (b.p. 30–60°). The solid was crystallized from ether–hexane as white needles (600 mg, 23% yield) m.p. 81–84°. Three crystallizations from hexane afforded analytically pure IV, m.p. 93–94·5°; λ_{max}^{Nujol} 4·78μ (−N_3), 5·69 (β-lactam carbonyl); NMR ($CDCl_3$) τ: 2·25–2·75 (m, 5H) 5·3 (s, 1H) 5·85 (d, each signal split into triplet, J_{gem} 14 c/s, J_{vic} 3·5 c/s, 1H) 6·6–7·5 (m, 3H) and 7·9–8·4 (m, 2H). (Found: C, 55·50; H, 4·63; N, 21·45; S, 12·42; $C_{12}H_{12}N_4SO$ requires: C, 55·38; H, 4·65; N, 21·53; S, 12·29%).

2-(p-*Nitrophenyl*) 5,6-*dihydro*-4H-1,3-*thiazine* (III)

(a) 3-Hydroxypropyl-*p*-nitrobenzamide was prepared by the acylation of 3-aminopropanol with *p*-nitrobenzoyl chloride, m.p. 92° (lit. m.p. 95–96°,[10] 103°[11]).

(b) 3-Hydroxypropyl-*p*-nitrobenzamide (15 g), P_2S_5 (17·5 g) and xylene (300 ml) were refluxed with constant stirring for 1½ hr. The xylene layer was decanted. The dark residue was treated with 25–30 ml of 10% NaOH aq and extracted with benzene. The combined organic extracts were successively washed with 10% NaOH aq and water. Removal of the solvent after drying over $MgSO_4$ afforded the title compound. Recrystallization from hexane gave 4·6 g of yellow plates m.p. 128–130°; λ_{max}^{Nujol} 6·3 μ (C=N). III was used for the next operation without further purification.

7-*Azido*-6-(p-*nitrophenyl*) *cepham* (V)

The title compound was prepared in 55% yield from HI[3] and azidoacetyl chloride by essentially the same procedure as described for the synthesis of IV. Crystallization from hexane gave the analytically pure product, m.p. 125–126° d; λ_{max}^{Nujol} 4·78 μ (—N_3), 5·65 (β-lactam carbonyl); NMR (C_6D_6) τ: 2·02 (d, 2H, J = 9 c/s), 2·75 (d, 2H, J = 9 c/s), 5·42 (s, 1H), 6·25 (m, 1H), 7·45 (m, 1H), 7·95 (m, 2H), 8·82 (m, 2H). (Found: C, 46·81; H, 3·79; N, 23·19; $C_{12}H_{11}N_5O_3S$ requires: C, 47·22; H, 3·63; N, 22·92%).

7-Amino-6-phenylcepham (VI)

A mixture of IV (0·9 g) and Adams catalyst (1·5 g) in 75 ml EtOAc was shaken with H_2 at 40 lb/in^2 at room temp for 56 hr. The soln was then filtered, solvent removed under reduced press and residue crystallized from ether as a pale yellow solid m.p. 81–83° (450 mg, 55·5%); λ_{max}^{Nujol} 2·9 and 3·0 μ (NH_2), 5·71 μ (β-lactam carbonyl), NMR ($CDCl_3$) τ: 2·32–2·75 (m, 5H), 5·52 (s, 1H), 5·6–6·1 (d, each signal split into a triplet, J_{gem} = 14 c/s and J_{vic} 3·5 c/s, 1H), 6·65–7·5 (m, 3H), 7·9–8·45 (m, 2H), 8·83 (broad s, 2H).

7-Phenoxyacetamido-6-phenylcepham VII

To an ice cold soln of VI (500 mg) and Et_3N (260 mg) in 25 ml CH_2Cl_2 was added with stirring a soln of phenoxy acetyl chloride (420 mg) in 15 ml CH_2Cl_2 over a period of 10 min. The mixture was allowed to come to room temp and left overnight. The suspension was then successively washed with water, dil $NaHCO_3$ aq and water. The organic layer was dried over Na_2SO_4. Removal of the solvent afforded solid residue of VII. Two crystallizations from ether yielded 620 mg of pure product, m.p. 151–153°; λ_{max}^{Nujol} 3·0 μ (NH), 5·7 μ (β-lactam carbonyl), 5·92 (amide carbonyl), NMR ($CDCl_3$) τ: 2·3–3·55 (m, 11H), 4·49 (d, 1H, J = 9 c/s), 5·69–6·01 (m, 2H, J = 15 c/s), 6·6–7·5 (m, 3H), 7·9–8·4 (m, 2H). (Found: C, 65·38; H, 5·64; N, 7·52; $C_{20}H_{20}N_2SO_3$ requires: C, 65·21; H, 5·47; N, 7·61%).

2-Phenyl-4-methyl-4-hydroxy-5,6-dihydro-4H-1,3-thiazine (VIII)[7]

A mixture of thiobenzamide (2·48 g), methyl vinyl ketone (1·68 g) and Et_3N (0·36 g) in t-butanol (20 ml) was stirred at 20° for 4 days. The solid that separated was filtered, washed with ether and recrystallized from t-butanol–benzene to give VIII m.p. 130–132° (lit.[7] m.p. 134°) yield 2·46 g. NMR ($CDCl_3$–CD_3COCD_3), τ: 2·1–2·8 (m, 5H), 6·1 (broad s, 1H), 6·85 (m, 2H), 8·15 (m, 2H), 8·58 (s, 3H).

2-Methyl-2-mercaptopropiophenone (XII)

A soln of Et_3N (15 ml) in CH_2Cl_2 (300 ml) was cooled to −10° and saturated with H_2S. To this cooled soln was added with constant stirring 20 g of 2-bromo-2-methylpropiophenone[12] over a period of 1 hr. The reaction mixture was stirred at −10° for additional 2 hr; brought to room temp and stirring continued for 4 hr. It was then washed with 300 ml 2N HCl, water and dried over Na_2SO_4. Removal of the solvent under reduced press followed by distillation afforded 12 g of the title compound, b.p. 81–84°/0·35 mm; λ_{max}^{neat} 3·91 μ (SH), 5·98 μ (C=O), NMR (CCl_4) τ: 1·9–2·8 (m, 5H), 7·7 (s, 1H), 8·4 (s, 6H).

For analysis the 3,5-dinitrobenzoyl derivative of XII was prepared by treating XII in CH_2Cl_2 soln with 3,5-dinitrobenzoyl chloride in the presence of Et_3N. It was crystallized from CH_2Cl_2–ether as pale yellow needles, m.p. 130–132°. (Found: C, 54·35; H, 3·87; N, 7·42; $C_{17}H_{14}N_2O_6S$ requires: C, 54·55; H, 3·77; N, 7·48%).

2,2-Dimethyl-3-phenyl-5,6-dihydro-1,4-thiazine XIII

A soln of 5 ml aziridine[13] in 10 ml Me_3N was heated to 60° and 5 g 2-methyl-2 mercaptopropiophenone was added over a period of ½ hr with constant stirring. The mixture was set aside for 3 hr at 60°. Removal of the solvent and vacuum distillation of the crude product afforded analytically pure dihydrothiazine (3·5 g, b.p. 100–104°/0·025 mm); λ_{max} 6·12 μ (C=N); NMR (CCl_4) τ: 2·8 (s, 5H), 6·08 (t, 2H, J = 5·5 c/s), 7·31 (t, 2H, J = 5·5 c/s), 8·58 (s, 6H). (Found: C, 70·09; H, 7·26; N, 6·63; $C_{12}H_{15}NS$ requires: C, 70·22; H, 7·37; N, 6·82%).

The β-lactam XIV (m.p. 109–112°) was obtained from XIII (2·7 g) by the addition of azidoacetyl chloride (1·8 g) in the presence of Et_3N (1·55 g) by using the method described for IV. The crude product (2·74 g) on chromatography over 220 g florisil using CH_2Cl_2 as the eluent afforded 950 mg of the pure compound; λ_{max}^{Nujol} 4·77 μ (N_3), 5.7 μ (β-lactam carbonyl); NMR ($CDCl_3$), τ: 2·62 (s, 5H), 5·42 (s, 1H), 5·5–7·6 (m, 4H), 8·28 (s, 3H), 8·85 (s, 3H). (Found: C, 58·81; H, 5·72; N, 19·31; $C_{14}H_{16}N_4OS$ requires: C, 58·32, H, 5·59; N, 19·44%).

The β-lactam XIV (300 mg) was converted to the corresponding lactam XV by hydrogenolysis using Adams catalyst (600 mg). The amino compound (150 mg) was crystallized from CH_2Cl_2–ether as pale yellow needles, m.p. 140–142° and was used as such for the next step; λ_{max}^{Nujol} 2·95 and 3·0 μ (NH_2), 5·70 μ (β-lactam carbonyl); NMR ($CDCl_3$), τ: 2·67 (s, 5H), 5·58 (s, 1H), 5·6–7·8 (m, 4H), 8·28 (s, 3H), 8·81 (s, 5H).

The β-lactam XV (262 mg) was acylated with phenoxy acetyl chloride. The product XVI was crystallized from benzene–hexane as white glistening plates (300 mg) m.p. 173–175°; λ_{max}^{Nujol} 3·05 μ (NH), 5·65 μ (β-lactam carbonyl), 6·02 μ (amide carbonyl); NMR ($CDCl_3$), τ: 2·55–3·5 (m, 11H), 4·42 (d, 1H), 5·65 (s, 2H), 5·65–7·7 (m, 4H). (Found: C, 66·31; H, 6·10; N, 6·95; $C_{22}H_{24}N_2O_3S$ requires: C, 66·65; H, 6·10; N, 7·00%).

Azido-β-lactam XX was obtained in 10% yield as a yellow oil by using the method described earlier;

λ_{max}^{neat} 4·78 μ (N_3), 5·7 μ (β-lactam carbonyl); NMR (CCl_4), τ: 5·84 (s, 1H), 8·06 (s, 6H), 8·38 (s, 2H, 8·52 (s, 3H), 8·6 (s, 6H). Mass spectrum showed a peak at *m/e* 226 corresponding to the loss of N_2 from the molecular ion.

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[13] Supplied by K and K Laboratories, Inc., Plainview, New York.