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Strained Heterocyclic Compounds. 10. Introduction of an Amide Side Chain in Place of Halogen in 7-Halo-8-oxo-1-azabicyclo[4.2.0]octane

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The nucleophilic displacement reaction between thallium(I) phthalimide and the bromo-β-lactams *2a*—*b* has been studied. The corresponding phthalimido-β-lactams *3a*—*b* were obtained in good yields with 90 % stereoselectivity (inversion at the C-7 carbon atom). The chloro-β-lactam *2c* reacted only in very low yield under the same conditions. Hydrazinolysis of the phthalimido-β-lactam *3a* and subsequent acylation gave a β-lactam *5a* with an amido side chain, appropriate for a penicillin analogue.

In the effort of synthesising penicillin analogs with modified nuclei [1] we have developed a general method for the synthesis of α-halo-β-lactams (*2*) by thermolysis of phenyl mercury compounds (*1*).[2] Other routes to halo-β-lactams are the addition of haloketenes to imines [3] and the base-induced bromination of cepham derivatives.[4]

These methods all give predominantly the thermodynamically more stable *trans*-isomer of the halo-β-lactams [2—4] (*i.e trans*-configuration of the hydrogens at the carbon atoms C-6 and C-7, *cf.* Fig. 1). However, in all the biologically active penicillins and cephalosporins the configuration at the corresponding sites is *cis*.[5] We have therefore searched for a general displacement reaction, exchanging the halogen for an amino function, that proceeds with inversion at the C-7 carbon atom.

After trying various reagents we found that *N*-phthalimidothallium fulfilled the requirements.[6] This reagent effected substitution of the halo-β-lactams *2a*—*b* in fairly good yields and with 90 % stereospecificity. Hydrazinolysis of the phthalimido-β-lactams *3a*—*b* gave the corresponding amino-β-lactams *4a*—*b*, which were acylated to the amido-β-lactams *5a*—*b*.

Similar substitutions have been attempted by several workers.[4,7—9] In one successful case 7-bromocephams were reacted with sodium azide to yield azido-β-lactams, which were reduced to yield the corresponding amino-β-lactams.[4] This method was not successful with the compounds *2a*—*b*.[6]

RESULTS AND DISCUSSION

Reaction between the halo-β-lactams 2a—c *and N-phthalimidothallium.* The formation of the phthalimido-β-lactams *3a*—*b* from *N*-phthalimidothallium and the *trans*-bromo-β-lactam *2a* in DMSO was studied in some detail. The reaction temperature showed a strong influence on the yield (*cf.* Table 1). At the optimum temperature of 150 °C the highest yield of *3* was obtained and after a 10 h reaction time 80 % of the starting material could be accounted for. The product β-lactams *3* were thermally quite stable to isomerisation and decomposition at 150 °C while the starting bromo-β-lactam *2a* decomposed rapidly when heated in DMSO at this temperature. *N*-Phthalimidothallium, however, stabilized the bromo-β-lactam due to its ability to trap released hydrogen bromide.

The stereoselectivity of the displacement reaction was also dependent on the temperature, the ratio of phthalimido-β-lactams *3a* to *3b* in the product decreasing from >10 at

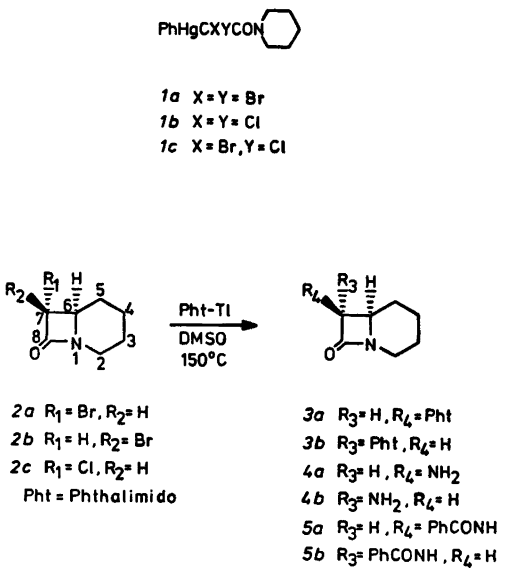

Fig. 1.

100 °C to 2 at 189 °C (*cf.* Table 1). The epimerisation observed may be due to isomerisation prior to substitution of the starting bromo-β-lactam *2a*. Further, as *cis*-phthalimidopenicillanates are known to epimerise irreversibly to their corresponding *trans*-isomers in the presence of bases [10] it is also possible that *N*-phthalimidothallium was sufficiently basic to cause the isomerisation of the β-lactam *3a* to yield *3b*. This would also explain the lack of epimerisation product in the formation of the *trans*-phthalimido-β-lactam *3b* from the *cis*-bromo-β-lactam *2b* (*cf.* below).

The configurations of the respective phthalimido-β-lactams *3a–b* were determined by ^{1}H NMR methods. Thus for the isomer *3a* the coupling constant for the C-6 and C-7 protons was larger than the corresponding coupling constant for the isomer *3b*. Accordingly the isomer *3a* was assigned the *cis*-configuration and the isomer *3b* the *trans*-configuration.[11]

The reaction time was also of importance both for the yield and the stereoselectivity (*cf.* Table 2), as longer reaction times are expected to favour both isomerisation and decomposition as well as substitution.

The reaction between the *cis*-bromo-β-lactam *2b* and *N*-phthalimidothallium in DMSO at 150 °C proceeded in considerably lower yield. The product *trans*-phthalimido-β-lactam *3b* was free from the *cis*-isomer *3a* according to ^{1}H NMR. Thus a reaction time of 2 h yielded 7 % of the product *3b* while 35 % of the *cis*-bromo-β-lactam *2b* was recovered. Extension of the reaction time to 11 h increased the yield of *3b* to 24 % while no bromo-β-lactam was recovered.

Substitution of the more stable *trans*-chloro-β-lactam *2c* was less successful (*cf.* Ref. 8). Thus the β-lactam *2c*, when reacted with *N*-phthalimidothallium in DMSO at 150 °C for 11 h gave only a 4 % yield of the product *3a*. Other polar, aprotic solvents were tried, *e.g* sulfolane and HMPA, but the yields of *3a* were still low (~5 %) when all the starting chloro-β-lactam was consumed.

As potassium phthalimide was more reactive than *N*-phthalimidothallium towards *N*-(haloacetyl)piperidines [12] this reagent was tried in the chloro-β-lactam system. However, after 2 h at 150 °C in DMSO only a trace of the product *3a* was obtained, while more than 50 % of the starting chloro-β-lactam was consumed.

Table 1. Temperature as an influencing factor for the isolated yield of phthalimido-β-lactams *3a–b* and the ratio of isomers *3a* to *3b* in the product from the reaction of *N*-phthalimidothallium with the *trans*-bromo-β-lactam *2a* in DMSO.

Temp. (°C)	Time (h)	Yield (%)	Ratio *3a/3b*
50	18	0	
100	4	5	> 10/1
150	10	55	10/1
189	1	38	2/1

Table 2. Reaction time as an influencing factor for the isolated yield of the phthalimido-β-lactams *3a–b* and the ratio of isomers *3a* to *3b* in the product from the reaction of the *trans*-bromo-β-lactam *2a* with *N*-phthalimidothallium in DMSO at 150 °C.

Time (h)	Yield (%)	Ratio *3a/3b*
2	18	> 10/1
7	34	> 10/1
10	55	10/1
16	36	3/1

Transformation of the phthalimido-β-lactams 3a–b *to the benzamido-β-lactams* 5a–b. Reaction of the β-lactam *3a* with anhydrous hydrazine in dichloromethane at room temperature [13] afforded the phthalic hydrazide salt of the amino-β-lactam *4a*. The free amino-β-lactam was obtained by the decomposition of this salt by treatment with dilute hydrochloric acid,[14] followed by removal of the phthalic hydrazide and subsequent basification. The yield of the crude amino-β-lactam *4a* by this method was 64 % and is not optimized. No purification was attempted of the amino-β-lactam, which was characterized by its spectroscopic data. Other methods for the hydrazinolysis were tried; thus treatment with hydrazine hydrate in refluxing dioxane [15] caused partial destruction of the β-lactam. The use of tetrahydrofuran or dioxan as the solvent at room temperature afforded lower yields of the amino-β-lactam.

Acylation of the crude amino-β-lactam *4a* to the benzamido-β-lactam *5a* could be effected with benzoyl chloride and triethylamine in tetrahydrofuran [16] or with benzoic acid and *N,N'*-dicyclohexylcarbodiimide in dichloromethane,[17] the last method giving a slightly better yield (47 % and 53 %, respectively). Thus the overall yield for the transformation of the phthalimido-β-lactam *3a* to an amido-substituted β-lactam *5a* was 26 %.

No isomerisation of the β-lactams *3–5* was detected throughout the reaction sequence, which is important for retaining the desired *cis*-configuration in the penicillin analogs. Thus the amino-β-lactam *4a* showed the typical coupling constant of 4 Hz for the H-7 and H-6 proton coupling of *cis*-β-lactams.[11] For the amido-β-lactam *5a* the coupling pattern for the H-7 proton was more complex due to the additional coupling of this proton with the NH-proton with a coupling constant of 7 Hz, characteristic of the NH and H-7 coupling constant in this type of compound.[18] By effecting the same transformations on the *trans*-phthalimido-β-lactam *3b* the amino-β-lactam *4b* and the benzamido-β-lactam *5b* were obtained. In these compounds the chemical shifts of the H-7 protons were at higher field than in the corresponding *cis*-compounds *4a* and *5a*, respectively. They also showed the characteristically smaller coupling constant (1.5-2 Hz) for the C-6 and C-7 protons of *trans*-β-lactams,[11] while in *5b* the coupling constant for the NH and C-7 protons were of the same magnitude (7 Hz) as in *5a*.

EXPERIMENTAL

All melting points were determined on a micro hot stage apparatus and are uncorrected. Elemental analyses were carried out by Mikroanalyslaboratoriet, Uppsala, Sweden. IR-spectra were recorded using a Perkin-Elmer Model 421 spectrophotometer. ^{1}H NMR spectra were recorded using a Varian A60 and a Varian EM360 instrument. The chemical shifts are given as δ-values relative to TMS as internal standard. Mass spectra were recorded using an LKB 9000 mass spectrometer. Column chromatography was performed using silica gel (Merck 0.05–0.2 mm). Preparative thin layer chromatography was performed using silica gel (Merck Fertigplatten 2 mm). All the DMSO used was distilled prior to use.

N-*Phthalimidothallium*. To a solution of 2.95 g (0.02 mol) phthalimide in 50 ml of dry THF was added 5.0 g (0.02 mol) of thallium(I) ethoxide. The reaction mixture was stirred for 3 h at room temperature. The precipitate formed was collected by filtration and washed with dry benzene. Yield 6.8 g (97 %), m.p. 310–312 °C (dec.). IR, λ_{max} (KBr): 3030, 1680, 1610–1530 (broad) cm^{-1}. ^{1}H NMR (DMSO): δ 7.43 (s, aromatic protons). MS, *m/e*: 349, 351 (M^+), 203, 205 (Tl^+).

cis-*7-Phthalimido-8-oxo-1-azabicyclo[4.2.0]-octane* (3a). *trans*-7-Bromo-8-oxo-1-azabicyclo-[4.2.0]octane (*2a*) [2a] (0.48 g, 2.3 mmol) and *N*-phthalimidothallium (0.84 g, 2.3 mmol) were heated in DMSO (30 ml) at 150 °C for 10 h. The solvent was evaporated *in vacuo* and the residue was dissolved in chloroform. The solution was washed with water and a saturated $NaHCO_3$ solution, dried over $CaCl_2$ and the solvent was evaporated. Separation of the reaction products in the residue was accomplished by chromatography on a column of silica gel, cooled to −20 °C by circulating ethanol. Elution with dry diethyl ether afforded phthalimide (0.055 g, 16 %), *trans*-7-bromo-8-oxo-1-azabicyclo[4.2.0]octane (*2a*) (0.114 g, 24 %), *trans*-7-phthalimido-8-oxo-1-azabicyclo[4.2.0]octane (*3b*) (0.035 g, 5 %), and the required product *cis*-7-phthalimido-8-oxo-1-azabicyclo[4.2.0]octane (*3a*) in 50 % yield (0.311 g). M.p. 174–176 °C. (Found: C 66.3; H 5.2; N 10.0. Calc. for $C_{15}H_{14}N_2O_3$: C 66.6; H 5.2; N 10.3). IR, λ_{max} (KBr): 1760, 1725 (>C=O) cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 1.4–2.0 (m, H-3, H-4, H-5), 2.5–4.2 (m, H-2, H-6), 5.39 (two doublets $J=1.5$ and $J=4.5$ Hz, H-7) and 7.96 (m, aromatic protons). MS, *m/e*: 270 (M^+), 123 ($M-C_6H_5NO_2$).

trans-7-Phthalimido-8-oxo-1-azabicyclo[4.2.0]-octane (3b). *cis*-7-Bromo-8-oxo-1-azabicyclo-[4.2.0]octane (*2b*)[2a] (0.20 g, 1 mmol), freshly purified by preparative TLC and *N*-phthalimidothallium (0.35 g, 1 mmol) were heated in DMSO (10 ml) at 150 °C for 11 h. Work-up as above followed by separation of the products by preparative TLC with diethyl ether as eluent gave *trans*-7-phthalimido-8-oxo-1-azabicyclo[4.2.0]octane (*3b*) (0.067 g, 24 %). M.p. 183–184 °C. (Found: C 66.5; H 5.2; N 9.9. Calc. for $C_{15}H_{14}N_2O_3$: C 66.6; H 5.2; N 10.3). IR, λ_{max} (KBr): 1760, 1725 (>C=O) cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.2–2.2 (m, H-3, H-4, H-5), 2.5–4.2 (m, H-6, H-2), 5.08 (d, $J=1.8$ Hz, H-7), and 7.91 (m, aromatic protons). MS, *m/e*: 270 (M^+).

Reaction between trans-*7-chloro-8-oxo-1-azabicyclo[4.2.0]octane* (2c) *and N-phthalimidothallium.* (A). *trans*-7-Chloro-8-oxo-1-azabicyclo-[4.2.0]octane (*2c*)[2b] (0.16 g, 1 mmol) and *N*-phthalimidothallium (0.35 g, 1 mmol) were heated in DMSO (10 ml) at 150 °C for 11 h. The reaction mixture was worked up and the products were separated as described above, yielding unreacted chloro-β-lactam (*2c*) and *cis*-7-phthalimido-8-oxo-1-azabicyclo[4.2.0]-octane (*3a*) (0.011 g, 4 %).

(B). As in (A) but with 10 ml HMPA, freshly distilled in a nitrogen atmosphere, as the solvent. A reaction period of 7 h gave the β-lactam *3a* (0.015 g, 6 %).

(C). As in (A) but with 10 ml freshly distilled sulfolane as the solvent and a reaction time of 8 h. The yield of the β-lactam *3a* was 0.005 g (2 %).

Reaction between trans-*7-chloro-8-oxo-1-azabicyclo[4.2.0]octane and potassium phthalimide. trans*-7-Chloro-8-oxo-1-azabicyclo[4.2.0]octane (*2c*)[2b] (0.16 g, 1 mmol) and potassium phthalimide (0.185 g, 1 mmol) were heated in DMSO (10 ml) at 150 °C for 2 h. The usual work-up and separation procedures yielded the unreacted *trans*-chloro-β-lactam (*2c*) (0.076 g, 48 %) and traces of the *cis*-phthalimido-β-lactam *3a* (by TLC, MS).

cis-*7-Amino-8-oxo-1-azabicyclo[4.2.0]octane* (4a). *cis*-7-Phthalimido-8-oxo-1-azabicyclo-[4.2.0]octane (*3a*) (0.270 g, 1 mmol) and 95 % hydrazine (0.067 g, 2 mmol) were stirred in dry dichloromethane (25 ml) at room temperature for 24 h. The solvent was evaporated *in vacuo*. The phthalic hydrazide-amino-β-lactam salt was stirred in 0.2 N HCl (6 ml) for 1 h at room temperature and the undissolved phthalic hydrazide (0.134 g, 83 %) was filtered off and washed with water. The acidic filtrate was combined with the washings and washed with dichloromethane to remove the unreacted phthalimido-β-lactam *3a* (0.005 g, 3 %), then made basic with potassium carbonate and extracted five times with dichloromethane. The dichloromethane phase was washed with water, dried over Na_2SO_4 and the solvent was evaporated to yield the *cis*-amino-β-lactam *4a* as an oil (0.090 g, 64 %). IR, λ_{max} (film): 3385, 3310 ($-NH_2$), 1737 (>C=O) cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.1–2.1 (m, H-3, H-4, H-5), 1.87 (s, NH_2), 2.3–4.0 (m, H-2, H-6) and 4.20 (dd, $J=4.5$ Hz and 2.0 Hz, H-7). MS, *m/e*: 140 (M^+), 84.

trans-*7-Amino-8-oxo-1-azabicyclo[4.2.0]octane* (4b). The *trans*-amino-β-lactam *4b* was obtained from the corresponding *trans*-phthalimido-β-lactam *3b* in the same manner as described above. The yield was 60 %. IR, λ_{max} (film): 3375, 3300 (NH_2), 1742 (>C=O) cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.1–2.2 (m, H-3, H-4, H-5), 2.06 (s, NH_2), 2.3–4.0 (m, H-2, H-6) and 3.67 (d, $J=2$ Hz, H-7). MS, *m/e*: 140 (M^+), 84.

cis-*7-Benzamido-8-oxo-1-azabicyclo[4.2.0]-octane* (5a). To *cis*-7-amino-8-oxo-1-azabicyclo-[4.2.0]octane (*4a*) (0.17 g, 1.2 mmol) and benzoic acid (0.087 g, 1.2 mmol) in dry dichloromethane (20 ml) cooled to 0 °C was added *N,N'*-dicyclohexylcarbodiimide (0.150 g, 1.2 mmol). The reaction mixture was then stirred at room temperature overnight. The *N,N'*-dicyclohexylurea was removed by filtration and the filtrate was washed with an aqueous saturated $NaHCO_3$ solution and then with water, dried over Na_2SO_4, and the solvent was evaporated. The crude product was chromatographed on a column of silica gel, with diethyl ether as the eluent to give *cis*-7-benzamido-8-oxo-1-azabicyclo[4.2.0]octane (*5a*) (0.081 g, 53 %). M.p. 203–204 °C. (Found: C 69.2; H 6.6; N 11.2. Calc. for $C_{14}H_{16}N_2O_2$: C 68.8; H 6.6; N 11.5). IR, λ_{max} (KBr): 3310 (–NH–), 1730 (>C=O, β-lactam), 1670 (>C=O, amide) cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.0–2.1 (m, H-3, H-4, H-5), 2.3–3.9 (m, H-2, H-6), 5.52 (dq, $J_{NH}=7$ Hz, $J_{H-6}=4$ Hz, $J_{H-5}=1.5$ Hz, H-7), 7.38 (m, H-3′, H-4′, H-5′), 7.83 (m, H-2′, H-6′) and 8.12 (d, $J=7$ Hz, NH). MS, *m/e*: 244 (M^+), 122, 150, 84.

trans-*7-Benzamido-8-oxo-1-azabicyclo[4.2.0]-*(5b). The *trans*-benzamido-β-lactam (*5b*) was obtained from the corresponding *trans*-amino-β-lactam *4b* in the same manner as above. The yield was 51 %. M.p. 210–211 °C. (Found: C 68.7; H 6.5; N 11.1. Calc. for $C_{14}H_{16}N_2O_2$: C 68.8; H 6.60; N 11.5). IR, ν_{max} (KBr): 3275 (>NH), 1750 (>C=O, β-lactam), 1645 (>C=O, amide) cm^{-1}. ^1H NMR ($CDCl_3$): δ 0.9–2.0 (m, H-3, H-4, H-5), 2.3–4.0 (m, H-2, H-6), 4.76 (dd, $J_{NH}=7$ Hz, $J_{H-6}=1.5$ Hz, H-7), 7.40 (m, H-3′, H-4′, H-5′), 7.86 (m, H-2′, H-6′) and 7.92 (d, $J=7$ Hz, NH). MS, *m/e*: 244 (M^+), 122, 105, 84.

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