Strained Heterocyclic Compounds. 5. The Synthesis of [Bromochloro(*N*,*N*-pentamethylenecarbamoyl)methyl]-phenylmercury and Its Thermal Decomposition to a Chloro-β-lactam

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In the last few years considerable efforts have been devoted to the synthesis of compounds related to penicillin.[1] Our own efforts have been directed towards the synthesis of penicillin analogues in which the thiazolidine nucleus has been modified. We have recently been able to synthesize bromo-β-lactams like *3* and *4* by thermolysis of phenylmercury compounds of the type *2* in boiling bromobenzene.[2] While the compound *3* could be prepared in good yield,[2b] only a low yield of the compound *4* was obtained.[2c] One reason for this is the low thermal stability of the compound *4*. Since the analogous chloro compound *4a* is considerably more stable,[3] attempts were made to prepare a chloro-β-lactam by thermolysis of the dichloro compound *2b*. However, due to the sluggishness of this reaction, the product chloro-β-lactam was extensively decomposed despite its relative stability.[2b] To circumvent these difficulties we have now prepared the bromochloro compound *2a*, which on thermolysis gave the desired chloro-β-lactam *3a* in good yield.

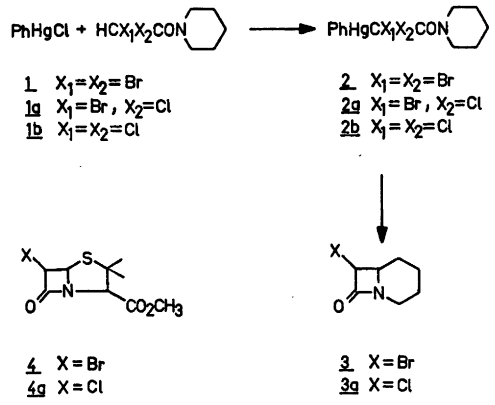

Fig. 1.

The phenylmercury compound *2a* was prepared essentially as the compounds *2* and *2b*. Bromochloroacetyl chloride, prepared by distillation of 1,2-dibromo-1,2-dichloro-1-ethoxyethane,[4] was reacted with piperidine to give the amide *1a*. This was condensed with phenylmercury chloride in THF using potassium *t*-butoxide as a base.[2] Interestingly, the condensation of the bromochloroamide *1a* and phenylmercury chloride gave lower yields than the corresponding reactions with either of the dichloro- and dibromoamides *1b* and *1*. Also, it is much more important that the reaction temperature is kept low with the bromochloroamide *1a*. A maximum yield of about 50 % of the compound *2a* was obtained when phenylmercury chloride and the bromochloroamide *1a* in THF solution were added rapidly from two dropping funnels to a cooled (−75°C) solution of the potassium *t*-butoxide in THF. If the butoxide and phenylmercury chloride are first mixed, the yield of condensation product is negligible. If the base and the bromochloroamide are first mixed, the yield of the mercury compound *2a* is lowered to about 20 %.

The thermal generation of the chloro-β-lactam *3a* from the mercury compound *2a* proceeded 10 times faster than the corresponding reaction from the dichloro analogue *2b*.[2b] In the reaction of the bromochloro compound *2a*, both phenylmercury chloride and bromide could be formed, although the elimination of phenylmercury bromide should be favoured (*cf.* Ref. 4b). Mass spectrometric analysis of the products gave no indication of the formation of phenylmercury chloride or bromo-β-lactam *3*.

The yield of the chloro-β-lactam *3a* from the compound *2a* is only slightly higher than the yield of the bromo-β-lactam *3* from the compound *2*. However, the exclusive generation of the *trans*-isomer of the chloro-β-lactam (*trans*:*cis* > 15:1) is an advantage since the correct configuration should be obtained on introduction of the proper side-chain (*cf.* Ref. 2). Furthermore, the facile generation of a relatively stable halogen derivative may be advantageous when labile systems of structures similar to *4a* are involved.

Experimental. All melting points were determined on a micro hot stage and are uncorrected. Elemental analyses were carried out by Centrala Analyslaboratoriet, Uppsala, Sweden, and by Alfred Bernhardt, Mikroanalytisches Laboratorium, 5251 Elbach über Engelskirchen, West Germany. IR spectra were recorded on a Perkin-Elmer No. 421 spectrophotometer, solids were measured in KBr discs, and oils as liquid films. The numbers are given in cm^{-1}. NMR spectra were recorded on a Varian A 60 instrument, the spectra refer to $CDCl_3$-solutions and the chemical shifts are given as δ-values relative to TMS as internal standard. Mass spectra were recorded on an LKB 9000 instrument. All THF used was freshly distilled from potassium metal/benzophenone under a N_2-atmosphere. Column chromatography was made on silica (Merck 0.05 – 0.2 mm) using increasing amounts of dry ether in distilled light petroleum as eluent.

N-(Bromochloroacetyl)piperidine (1a). Bromochloroacetyl chloride (38.4 g, 0.2 mol) in 200 ml of dry ether was added during 15 min from a dropping funnel to a magnetically stirred, ice-cooled solution of piperidine (34 g, 0.4 mol) in 800 ml dry ether. The reaction mixture was left for 3 h at room temperature and the precipitate of piperidine hydrochloride was filtered off. The ether solution was washed with two portions of 2 M HCl, two portions of saturated $NaHCO_3$-solution and one portion of water, then dried over Na_2SO_4 and evaporated. Recrystallization of the crude product from diethyl ether gave white crystals, m.p. 60–62°C. Yield 31.7 g (66 %). (Found: C 35.08; H 4.63; Br 33.07; Cl 14.61; N 5.77. Calc. for $C_7H_{11}BrClNO$: C 35.14; H 4.60; Br 33.05; Cl 14.64; N 5.85.) IR: CO 1635 cm^{-1}. NMR 1.68 (S, CH_2); 3.64 (S, $N-CH_2$); 6.34 (S, CHBrCl). MS: *m/e* 239, 241, 243 (M).

[Bromochloro(N,N-pentamethylenecarbamoyl)methyl]phenylmercury (2a). Phenylmercury chloride (3.1 g, 0.01 mol) in THF (80 ml) and *N*-(bromochloroacetyl)piperidine (2.4 g, 0.01 mol) in THF (50 ml) were added rapidly and simultaneously from two dropping funnels to a magnetically stirred solution of unsolvated *t*-BuOK (0.01 mol) in THF (100 ml), which was maintained at −75°C during the reaction. During the addition there was always a small excess of the amide over the phenylmercury chloride. When the addition was complete the reaction mixture was kept at −75 °C for an additional 45 min. The temperature was quickly raised to +10°C, and the solvent was evaporated on a rotatory evaporator at room temperature. The residue was dissolved in benzene (200 ml), washed with distilled water (40 ml) and dried over $MgSO_4$. Crystallization from dry diethyl ether gave [bromochloro(*N,N*-pentamethylenecarbamoyl)-methyl]phenylmercury (*2a*) 2.46 g (48 %), m.p. 111–113 °C (dec.). When the reaction was performed at −40 °C, the yield was lowered to 0.55 g (11 %). A longer reaction time also lowered the yield; thus, 75 min gave 1.26 g (27 %), 120 min gave 0.94 g (18 %). (Found: C 30.7; H 3.00; Br 16.0; Cl 7.14; N 2.69. Calc. for $C_{13}H_{15}BrClHgNO$: C 30.2; H 2.94; Br 15.5; Cl 6.85; N 2.71). IR: CO 1615 cm^{-1}. NMR: 1.75 (S, CH_2); 3.90 (S, $N-CH_2$); 7.60 (S, aromatic protons).

Thermolysis of [bromochloro(N,N-pentamethylenecarbamoyl)methyl]phenylmercury (2a). 0.8 g (1.55 mmol) of *2a* was refluxed in 240 ml freshly distilled bromobenzene. The decomposition of *2a* was followed by the use of IR spectrometry (β-lactam absorption at 1760 cm^{-1}) with samples removed after 1.3 h, 1.7 h, 2 h, 2.3 h, and 3.5 h. The best result was obtained at 2.3 h. The solvent was removed *in vacuo*, ether was added and the insoluble phenylmercury bromide was filtered off. Separation of the ether soluble products was accomplished by chromatography on a column of silica gel, cooled to −20 °C by cold circulating ethanol. Elution with increasing amounts of diethyl ether in light petroleum afforded 7-chloro-8-oxo-1-azabicyclo[4.2.0]octane (*3a*) (0.125 g, 54 %). Only the *trans*-isomer of *3a* could be detected by NMR: 1.2–1.3 (M, H-3, H-5); 2.6–4.1 (M, H-2, H-6); 4.45 (D, $J = 1.3$ Hz, H-7, *cf. cis*-isomer 4.95 (two D, $J = 1.4$ and 4.4 Hz, H-7).

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Synthesis of Bradykinin by Fragment Condensation on a Solid Support

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Solid phase peptide synthesis (SPPS) was introduced by Merrifield.[1] In a series of papers he developed the technique further and demonstrated the exceptional scope of his method.[2]

To simplify purification, which is the crucial step of this method, Weygand and one of the present authors [3] attempted to couple a peptide fragment instead of an amino acid derivative, *i.e.*, to use fragment condensation instead of a step-wise approach in analogy with common strategy in conventional peptide synthesis. We found that a peptide could be coupled satisfactorily with respect to the yield and with a very low degree of racemization when *N,N'*-dicyclohexylcarbodiimide (DCC) plus *N*-hydroxysuccinimide (HOSu) together [4] were used in CH_2Cl_2, the solvent of choice in SPPS, although admittedly the evidence concerning the yield was weak. Both considerations are of equally fundamental importance in this context. Since our initial work in this area, a couple of papers