Spiro- and Bicyclic Azalactams by Hydrolysis of α-Chlorinated Bicyclic Amidines

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The synthetic potential of α-chlorinated bicyclic amidines to form spiro- and bicyclic azalactams on hydrolysis has been investigated. Thus, **2a,b**, prepared by chlorination of **1a,b** with carbon tetrachloride in DMF, were treated with water *via* hydrolysis of the amidine function and an intramolecular substitution, **2a**, afforded the azaspirolactam **6a**, and **2b** gave the isomers **6b** and **6c** in the ratio 22:78, respectively. Similarly, α-chlorinated DBU **3b** gave the bicyclic azalactam **10**. A high-yield preparative method for obtaining the bicyclic amidine **1a** was worked out on the basis of Reissert's method from 1893, starting from diethylmalonate and α-bromopropylphthalimide.

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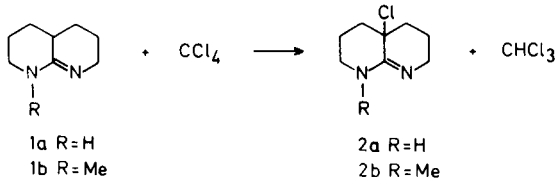
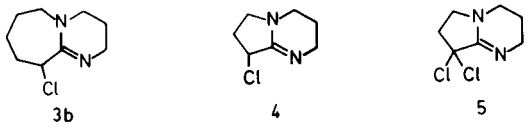
We recently reported on the reaction of bicyclic amidines with carbon tetrachloride, giving α-chlorinated amidines and chloroform, *e.g.*, **1** forming **2** [1]. On treatment with carbon tetrachloride, the commercially available DBU and DBN gave the corresponding α-chlorinated derivatives **3b**, **4** and **5**, respectively.

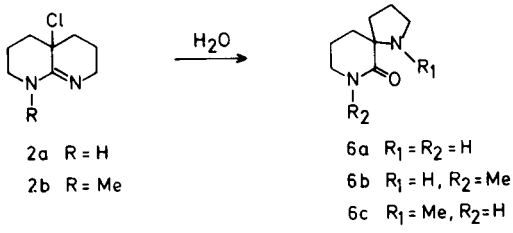




This new type of functionality has potential as precursor to interesting spiro- and bicyclic azalactams *via* hydrolysis and subsequent intramolecular displacement reaction of the chlorine by the amino group. We report here our results on the hydrolysis of three bicyclic α-chlorinated amidines, which demonstrate the facile formation of apparently new azalactams and the variation in product type due to the ring structure of the substrate. To obtain access to larger amounts of **1a**, we developed an improved synthesis of this compound, which is also reported [2].

In our investigations of the mechanism of the above-mentioned chlorinations, we found that these reactions are conveniently performed in DMF as solvent, giving a fast conversion and pure product. Previous experiments were performed in carbon tetrachloride or a mixture of benzene and carbon tetrachloride, *cf.* formation of **3b** in the experimental section.

The chlorinations of **1a** and **2b** were performed in DMF. After evaporation of the solvent, the α-chloroamidines **2a** and **2b**, respectively, were directly treated with water. After extraction and work-up, **2a** afforded the azalactam **6a**. The progress of the reaction was followed by ^{13}C-nmr, which showed that **6a** was formed as the major product (>70%).



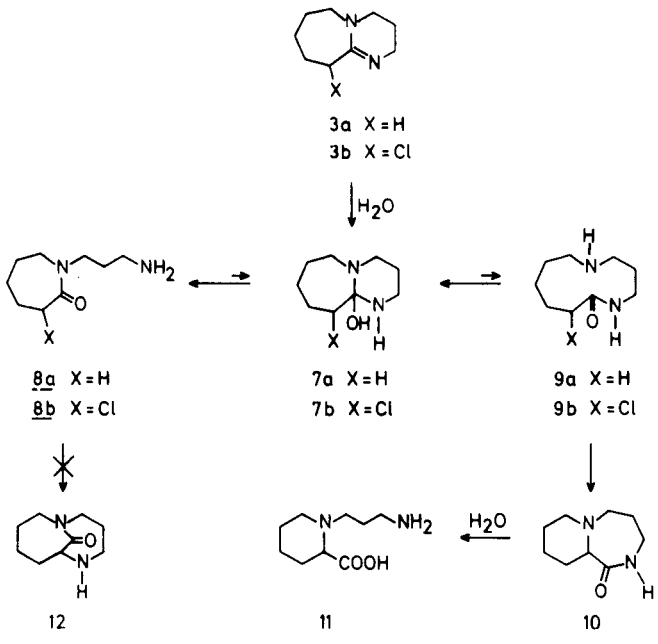
In contrast to **2a**, the *N*-methylated amidine **2b** has the possibility of forming two isomeric azaspiro lactams, and **2b** indeed gave **6b** and **6c**, in a 22/78 ratio, as measured by gc. Mainly ^{1}H-nmr and ir data were used to distinguish between **6b** and **6c**.

The hydrolysis of α-chlorinated DBU **3b** proved to be more complex. The primary product from **3b**, which was not isolated, transformed slowly with a half-life of about 2 days at room temperature into another compound. Spectroscopic data for this compound were in full agreement with the structure of the bicyclic azalactam **10** [3]. By warming an alkaline solution of **3b** for 6 hours, the product **10** was obtained in 70% yield. Prolonged warming gave gradual conversion into a compound, to which we ascribe the conjugate base of the amino acid structure **11**.

Previous studies of the hydrolysis of amidines [4] and transamidation reactions in cyclic aminoamide systems [5] have shown that, on treatment with aqueous potassium hydroxide, the amidine DBU **3a** gives only **8a** and none of the 11-membered isomeric **9a** [4], due to the instability of **9a** caused by transannular interactions. An attempt to

form **9a** from the 11-membered *N*-tosyl derivative led to isomerization to **8a** [5].

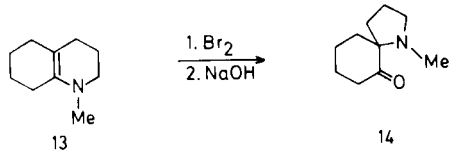
Accordingly, we propose that the initially formed product in the hydrolysis of **3b** is the 7-membered lactam **8b**, which, *via* the hemiorthoamide intermediate **7b** and **9b**, slowly reacts to **10** as shown in Scheme I.



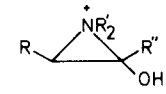
Scheme I

Structure **8b** is not likely to undergo ring closure to **12** by substitution of the chlorine since electronic conjugation in the amide function in **12** is lost. The formation of **10** thus indicates the formation of 11-membered azalactams, even if such a species is not directly observed.

Our results on the chlorination and hydrolysis of amidines are in conformity with the results on bromination and subsequent ring contractions of bicyclic enamines [6], *e.g.*, **13** giving 1-azaspiro compounds **14**.



In the rearrangement of the initially formed α-bromo iminium salts, the aziridinium ion **15** has been suggested as an intermediate [6]. There is a possibility that the corresponding aziridinium ion is involved in the transformation to **10** by direct reaction from **7b**. On basis of suggested rates, in the order of $> 10^5 - 10^7\ s^{-1}$, for cleavage of hemiorthoamides [7], we find it more likely that **10** is formed *via* **9b**.



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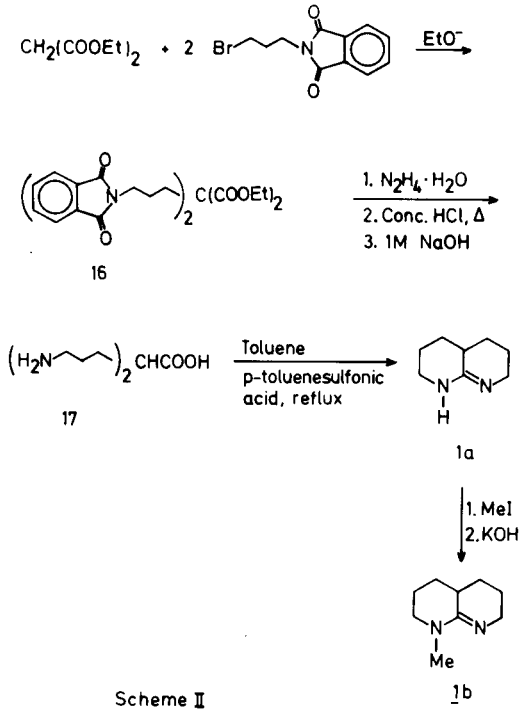
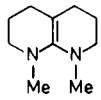
Our reaction mechanistic work on the chlorination of **1a** and the studies of the possible role of **1a** as a bifunctional catalyst in 1,3-proton transfer reactions [8a,b] required access to pure **1a** in large amounts. Accordingly, Reissert's method from 1893 [2] was improved into a high-yield preparative procedure, Scheme II, which is more efficient than our recently published novel amidine synthesis [9].



Scheme II

In this modification we employed hydrazine hydrate for removal of the phthalimide-protecting group [10] in **16** and neutralized the amino acid dihydrochloride with equimolar amounts of aqueous sodium hydroxide, instead of treatment with silver oxide and hydrogen sulfide. The ring-closure step to amidine was performed by refluxing the reaction mixture of amino acid **17** in toluene with catalytical amounts of *p*-toluenesulfonic acid under water separation [11]. Sublimation yielded **1a** in 71% yield from **16**. The *N*-methylated amidine **1b** [2,12] was then obtained by methylation of **1a** with methyl iodide. Amidine **1b** was found to be contaminated by a few per cent of **1a** and a compound which, on the basis of ^{13}C-nmr and mass spectra, we consider as the ketene aminal **18** formed through dimethylation of **1a**.



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EXPERIMENTAL

General Procedure.

All boiling points and melting points are uncorrected. The melting points were measured with a Leitz melting point microscope. The ^{1}H and ^{13}C-nmr spectra were recorded on a JEOL FX-100 spectrometer. The chemical shifts (δ values) are given in parts per million relative to the residual signal from the solvent as an internal standard, for hexadeuteriobenzene δ 7.25 in ^{1}H-nmr and δ 128.0 in ^{13}C-nmr and for deuteriochloroform δ 7.25 in ^{1}H-nmr and δ 77.0 in ^{13}C-nmr. Unless otherwise stated, the nmr spectra were recorded in hexadeuteriobenzene. Infrared (ir) spectra were determined on a Perkin-Elmer 177 spectrophotometer. Mass spectra were obtained with a LKB 9000 mass spectrometer at an ionizing energy of 70 eV. Relative intensities are given in parentheses after the m/e value. Analytical gas chromatography was performed on a Hewlett Packard 5880 A gas chromatograph with a silanized glass column packed with 10% Carbowax 20 *M*/1% potassium hydroxide on Chromosorb W-AW-DMCS. Preparative gas chromatography was performed on a Varian Aerograph 920 gas chromatograph with a glass column packed with 20% Carbowax 20 *M*/1% potassium hydroxide.

2,10-Diazabicyclo[4.4.0]dec-1-ene (**1a**) [2,9,13].

Diethyl di(3-phthalimidopropyl)malonate (**16**) was synthesized according to Reissert [2], mp 160.5-161.5° (lit 155.5° [2]), 76% yield. A solution of **16** (21.3 g, 0.040 mole) in 175 ml of ethanol was refluxed with 99-100% hydrazine hydrate (3.98 g, 0.080 mole) for 1.5 hours, 40 ml of water was added and the solvent evaporated. The yellow residue was refluxed in 75 ml of concentrated hydrochloric acid for 12 hours and twice diluted with water, filtered and evaporated. Excess hydrochloric acid was completely removed by the second evaporation. The phthalhydrazide formed in the hydrazinolysis can also conveniently be filtered off before hydrolysis and decarboxylation with hydrochloric acid. The hydrolysis product was neutralized with 80 ml of 1.0 *M* sodium hydroxide to give **17**, and the solvent was evaporated. The rotavapor was filled with nitrogen to protect **17**. The residue was refluxed for 6.5 hours in 60 ml of toluene and *p*-toluenesulfonic acid (20 mg) under nitrogen using a Dean-Stark water separator. Evaporation of the toluene gave a residue, which was sublimed at 65° (0.01 mm Hg) to give 3.89 g (71% based on **16**) of **1a**. Due to its high tendency to hydrolyse and to form carbonate, **1a** was stored under nitrogen, mp 85-86° [14]. The melting point previously given deviates considerably from that presented here, presumably due to the formation of **2a** during recrystallization of **1a** from carbon tetrachloride [9].

10-Methyl-2,10-diazabicyclo[4.4.0]dec-1-ene (**1b**) [2,12].

A solution of 4.0 g (0.029 mole) of **1a** in 25 ml of dry benzene was added to 5 ml of methyl iodide (freshly distilled, bp 41.5-42.0°) in 10 ml of dry benzene. The solution was refluxed under nitrogen for 45 minutes and then evaporated to dryness. The residue was stirred in 30 ml of benzene with a mixture of 20 g of finely powdered potassium hydroxide and 4.5 g of calcium oxide at room temperature for 25 minutes and the solution was then filtered under nitrogen. Evaporation and distillation gave 3.3 g (75%) of **1b**, with a few per cent of **1a** and probably **18** as impurities. Data for **1b** are: bp 100-102.5° (10 mm Hg); ir (neat): 1622 cm^{-1} (C=N); ^{1}H-nmr: δ 1.5 (m, 9H), 2.94 (s, 3H), 2.9-3.9 (m, 4H); ^{13}C-nmr: δ 24.5 (t), 25.1 (t), 29.2 (t), 31.0 (t), 36.3 (d), 37.7 (q), 48.6 (t), 52.3 (t), 159.5 (s); ms: m/e 152 (M$^+$, 100%).

1,7-Diazaspiro[4.5]decan-6-one (**6a**).

A solution of **1a** (0.88 g, 6.4 mmoles) in 70 ml of dry DMF and 12 ml of dry carbon tetrachloride was kept in the dark under nitrogen at room temperature for 4 days and the solution was then evaporated (oil pump) to yield **2a** (1.11 g, 6.4 mmoles), mp 119-120° dec, further data see ref [1]. Without further purification, **2a** was treated with 100 ml of water. After 2.5 hours at room temperature, the solution was basified and after another 0.5 hour extracted with dichloromethane, dried (potassium carbonate), filtered, and evaporated to give 0.29 g (30%) of **6a** after recrystallization from hexane, mp 91.0-92.0°; ir (Nujol): 3325, 3285, 3185, 3050 (NHC=O), 1650 (C=O) cm^{-1}; ^{1}H-nmr: δ 1.4-2.2 (m, 8H), 2.8 (m, 4H), 3.1 (m, 1H), 8.0 (br s, NHC=O, 1H); ^{13}C-nmr: δ 20.7, 27.5, 35.3, 38.6, 42.3, 47.9, 65.0, 177.5; ms: m/e 154 (M$^+$, 13%).

Anal. Calcd. for $C_8H_{14}N_2O$: C, 62.31; H, 9.15; N, 18.17. Found: C, 62.19; H, 9.17; N, 17.93.

6-Chloro-10-methyl-2,10-diazabicyclo[4.4.0]dec-1-ene (**2b**).

A solution of 1.09 g (7.2 mmoles) **1b** in a mixture of 50 ml of dry DMF and 10 ml of dry carbon tetrachloride was kept at 45° in the dark under nitrogen for 22 hours. The solution was evaporated (oil pump) to give 1.35 g of **2b** as a yellow liquid, which crystallized when placed in the freezer. Analysis showed impurities on the order of a few per cent, which originated from impurities in **1b**. Data for **2b** are: ir (neat): 1628 cm^{-1} (C=N); ^{1}H-nmr: δ 1.4-3.9 (m, 12H), 2.76 (s, 3H); ^{13}C-nmr: δ 19.6, 20.9, 38.4 (2 signals), 39.2, 48.0, 51.9, 62.8, 157.1; ms: m/e 186, 188 (M$^+$, 31 and 9.5%, respectively).

7-Methyl-1,7-diazaspiro[4.5]decan-6-one (**6b**) and 1-Methyl-1,7-diazaspiro[4.5]decan-6-one (**6c**).

Compound **2b** (1.35 g) from above was hydrolysed in 75 ml of water. After 4.5 hours at room temperature, the solution was basified with sodium hydroxide pellets (0.7 g) and after another 2 hours extracted with dichloromethane in a continuous extractor. The organic phase was dried (potassium carbonate) and evaporated, leaving a crude mixture (1.12 g) of **6b** and **6c** in the ratio 22:78 (gc analysis). Recrystallization from hexane gave 0.60 g (50%) of **6c**, mp 116-117°; ir (Nujol): 3270, 3175, 3050 (NHC=O), 1650 (C=O) cm^{-1}; ^{1}H-nmr: δ 1.3-2.4 (m, 8H), 2.58 (s, 3H), 2.85 (m, 2H), 3.1 (m, 1H), 3.5 (q, 1H), 8.4 (br s, 1H, NHC=O); ^{13}C-nmr: δ 22.0, 23.2, 35.0, 35.5, 39.7, 42.2, 56.4, 66.6, 176.1; ms: m/e 168 (M$^+$, 25%).

Anal. Calcd. for $C_9H_{16}N_2O$: C, 64.25; H, 9.59; N, 16.65. Found: C, 64.00; H, 9.57; N, 16.29.

The mother liquor from the recrystallization of **6c** was evaporated and the residue was purified by preparative gc to give 0.13 g (11%) of **6b** as a liquid; ir (neat): 3500, 3290, 1635 (C=O) cm^{-1}; ^{1}H-nmr: δ 1.3-2.3 (m, 8H), 2.5-2.9 (m, 3H), 2.71 (s, 3H), 2.82 (s, NH, 1H), 3.1 (m, 1H); ^{13}C-nmr: δ 20.6, 27.5, 35.1, 35.3, 38.6, 47.9, 49.9, 65.5, 174.4; ms: m/e 168 (M$^+$, 12%).

Anal. Calcd. for $C_9H_{16}N_2O$: C, 64.25; H, 9.59; N, 16.65. Found: C, 63.44; H, 9.56; N, 16.26.

6-Chloro-1,8-diazabicyclo[5.4.0]undec-7-ene (**3b**).

A solution of 2.60 g (17.1 mmoles) of **3a** in 8 ml of benzene and 15 ml of carbon tetrachloride was kept at 45° for 5.5 days. Evaporation yielded a dark liquid, which was distilled to afford **3b**, which solidified when kept in the freezer, 1.35 g (56%); bp 105-108° (0.01 mm Hg); ir (neat): 1612 cm^{-1} (C=N); ^{1}H-nmr: δ 1.4-1.9 (m, 8H), 2.4 (dd, 1H, J = 14.6 and 5.5 Hz), 2.8 (t, 2H, J = 6.1 Hz), 3.4 (t, 2H, J = 5.5 Hz), 3.8 (dd, 1H, J = 14.5 and 10.7 Hz), 5.0 (dd, 1H, J = 5.85 and 1.46 Hz); ^{13}C-nmr: δ 22.8 (t), 24.0 (t), 29.5 (t), 33.2 (t), 44.8 (t), 49.8 (t), 51.7 (dd), 66.4 (d), 156.9 (s); ms: m/e 186, 188 (M$^+$, 52 and 17% respectively), 151 (M − Cl, 100%).

1,5-Diazabicyclo[5.4.0]undecan-6-one (**10**).

Hydrolysis of **3b** (0.30 g, 1.6 mmoles) was performed in 50 ml of 0.5 *M* sodium hydroxide at 50° for 6 hours. The solution was extracted with dichloromethane and the organic phase was evaporated to give a residue, which was chromatographed over silicagel. Elution with ethanol-30% ammonia in water (7:3) yielded **10**, which, after sublimation (60°, 0.01 mm Hg) gave 0.19 g (70%), mp 131.5-132°; ir (Nujol): 3270, 3185, 3060 (NHC=O), 1650 (C=O) cm^{-1}; ^{1}H-nmr (deuteriochloroform): δ 1.5-1.8 (m,

8H), 2.3 (m, 1H), 2.6-3.2 (m, 5H), 3.5 (m, 1H), 7.3 (br s, 1H, CHN=O); ^{13}C-nmr (deuteriochloroform): δ 22.5, 26.4, 27.6, 29.2, 40.3, 52.7, 55.9, 66.9, 177.2; ms: m/e 168 (M^+, 24%).

Anal. Calcd. for $C_9H_{16}N_2O$: C, 64.25; H, 9.59; N, 16.65. Found: C, 64.17; H, 9.77; N, 16.27.

Acknowledgement.

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REFERENCES AND NOTES

[1] S. Löfås and P. Ahlberg, *J. Chem. Soc., Chem. Commun.*, 998 (1981).

[2] A. Reissert, *Chem. Ber.*, **26**, 2137 (1893); **27**, 979 (1894).

[3] Structurally related bicyclic azalactams have been shown to possess pharmacological activity and have been synthesized in various ways: M. E. Freed and A. R. Day, *J. Org. Chem.*, **25**, 2108 (1960); A. D. Lourie and A. R. Day, *J. Med. Chem.*, **9**, 311 (1966); T. Yamazaki, M. Nagata, K. Ogawa and F. Nohara, *Yakugaku Zasshi*, **87**, 668 (1967); *Chem. Abstr.*, **67**, 90770m (1967); L. A. Paquette and M. K. Scott, *J. Org. Chem.*, **33**, 2379 (1968); A. M. Likosherstov, L. S. Nazarova and A. P. Skoldinov, *J. Org. Chem. USSR (Engl)*, **6**, 1733 (1970); T. A. Crabb and R. F. Newton, *J. Chem. Soc., Perkin Trans. II*, 1920 (1972).

[4] C. Heidelberger, A. Guggisberg, E. Stephanou and M. Hesse, *Helv. Chim. Acta*, **64**, 399 (1981).

[5] A. Guggisberg, U. Kramer, C. Heidelberger, R. Charubala, E. Stephanou, M. Hesse and H. Schmid, *ibid.*, **61**, 1050 (1978).

[6] L. Duhamel, J. M. Poirier and P. Granger, *J. Org. Chem.*, **44**, 3576 (1979).

[7] C. L. Perrin and G. M. L. Arrhenius, *J. Am. Chem. Soc.*, **104**, 2839 (1982) and references therein.

[8a] K. Janné and P. Ahlberg, *J. Chem. Soc., Chem. Commun.*, 1040 (1976); [b] M. Ek and P. Ahlberg, *Chem. Scr.*, **16**, 62 (1980).

[9] K. Janné and P. Ahlberg, *Synthesis*, 452 (1976).

[10] H. R. Ing and R. F. H. Manske, *J. Chem. Soc.*, 2348 (1926).

[11] The ring-closure step from aminolactam has been performed in this way for other bicyclic amidines, *e.g.*, DBN and DBU: H. Oediger, F. Möller and K. Eiter, *Synthesis*, 591 (1972).

[12] Amidine **1b** has previously been obtained by cyclodehydrogenation of 3-(3-aminopropyl)-*N*-methylpiperidine; H. Möhrle and F. Specks, *Arch. Pharm.*, **308**, 499 (1975).

[13] IUPAC nomenclature; 1,2,3,4,4a,5,6,7-octahydro-1,8-naphthyridine.

[14] Spectroscopic data were identical with data for **1a** prepared according to ref [9], see however corrections in ref [1].