Formation of 1H-Aziridines from Chalcones and Hydroxylamine

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Highly substituted chalcones 1 do not react with two molecules of hydroxylamine affording dioximes 2 or hydroxyamino-oximes 3 as expected according to von Auwers' procedure\(^1\): only one molecule of hydroxylamine is consumed leading to trans-configurated 2-benzoyl-3-phenyl-1H-aziridines 4.

Schönenberger et al.\(^2\) have reported on cytostatic Pt-complexes of the 1,2-diamino-1,2-diphenylethane type. Especially meso-1,2-bis-(2,6-dichloro-4-hydroxyphenyl)ethylenediamine-dichloro-Pt(II) (5) is of interest as it shows low affinity to the estrogen receptor when compared with the Pt-free ligand, it has, however, an enhanced endocrinological activity.

In our first paper in this field\(^4\) we have touched on the conformational flexibility of Pt-complexes of 1,2-diamino-ethanes in comparison with that of 1,3-diaminopropane-Pt-complexes, prepared according to von Auwers\(^1\) by reacting chalcones with two molecules of hydroxylamine followed by reduction (Scheme 2 in lit.\(^5\)). Here we describe an anomaly of von Auwers' procedure:

When 0.1 mol of the chalcones 1 prepared from 2,6-dichloro-x-methoxybenzaldehydes 6 and 2,6-dichloror-x-methoxyacetophenones 7 (which in turn could not be prepared by Friedel-Crafts acylation but were obtained from 6a, 6b with H\(_2\)CMgI and subsequent oxidation) - were treated in a slightly modified von Auwers-procedure\(^1\) as described\(^4\) with 0.263 mol H\(_2\)NOH-HCl in water/KOH (Experim. and Lit.\(^4\)) we obtained ketones which contain one N-atom only. \(^1\)H-NMR spectra revealed that trans-configurated aziridines were formed: according to Brois\(^5\) \(^3\)J\(_{HCH}\) in cis-aziridines is always greater than that in trans-aziridines. For cis-aziridines J-values of 5.0 - 8.5 Hz are reported, whilst trans-isomers show 2.0 - 6.3 Hz. These data are corroborated by Weber and Lieper\(^6\). In our cases J = 3.0 Hz indicates trans-substitution. Under EI-conditions the mass spectra reveal prominent signals for (Ar-CH(NH)-CH\(^+\)), Ar-CO\(^+\), and Ar-CH\(_2\)\(^+\) ions.

von Auwers and Müller\(^1\) have assumed that the reaction of chalcones with hydroxylamine proceeds via a hydroxylamino-ketone which subsequently reacts with a second molecule of hydroxylamine (the authors could not trap the intermediate hydroxyamino-ketone under various conditions. We did not performe pertinent experiments). - The formation of our aziridines with a highly hindered benzoyl group (Cl-substituents in both o-positions) favours von

\(^{*}\) Respectfully dedicated to Prof. Zymalkowski, Bonn, at the occasion of his 80th birthday.

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**Scheme 1**

Auwers' hypothesis. Moreover, 2,6-dichloro-4-methoxybenzaldehyde (6a) and 2-chloro-4-methoxyacetophenone are smoothly converted to the pertinent oximes; 2,6-dichloro-4-methoxyacetophenone (7a) and 2,6-dichloro-3-methoxyacetophenone (7b) did not react with hydroxylamine under various conditions on a prep. scale (boiling with hydroxylamine in pyridine for 110 h afforded about 12% of the corresponding oxime (1H-NMR) in accordance with Laird).

We tried to prepare 1,3-bis-(2,6-dichloro-4-hydroxyphenyl)-1,3-diaminopropane (8), the CH₂-homologue of Schönberner's ligand [3] of complex 5, by converting chalcone 1a into the 1,3-dicarbonyl compound 9 (Scheme 3) by addition of Br₂ [10], substitution with OCH₃, HBr-elimination [11], and enolate cleavage, but 9 so obtained is completely enolized and does not react with hydroxylamine.

It is well known that in most cases 1,3-diketones yield isoxazoles when treated with hydroxylamine, but in some instances the isolation of dioximes in the reaction of hydroxylamine with β-diketones has been reported [8].

Chalcone aziridines are known already for a long time. They can be prepared by the reaction of chalcone dibromides with NH₃ [9], by reaction of chalcones with prim. amines in the presence of I₂ [10], and by 1,3-elimination of MeOH from 1,3-diaryl-3-methoxyamino-1-propanones [11].

In 1904 Wieland [9] obtained a chalcone aziridine from 2,3-dibromo-1-phenyl-3-(4-nitrophenyl)-1-propanone and NH₃, but he assumed that a piperazine derivative had been formed by ring closure of two molecules of dibromo-ketone and two molecules of NH₃. - Analogously, Ruhemann and Watson [12] prepared 2-benzoyl-3-phenylaziridine. They excluded a piperazine structure on account of the determination of the molecular mass and discussed a 2-amino-1,3-diphenyl-1-propen-3-one structure. So did Blatt [11] who obtained chalcone aziridines by the 1,3-elimination of MeOH (vide supra). Cromwell et al. [13] ascertained the aziridine character of the compounds obtained according to Wieland [9], Ruhemann [12], and Blatt [11] by their chemical and spectroscopic properties, and established trans-configuration of the compounds obtained by Blatt [11]. Cromwell's results [14] were corroborated by experiments concerning the mechanism of aziridine formation and spectroscopic measurements performed by Weber et al. [6].


According to Cromwell [14] chalcone aziridines are formed by 1,4-addition of O-methyl-hydroxylamine to the chalcone, followed by deprotonation at C-2 to a resonance-stabilized carbonium and intramolecular nucleophilic attack at the N-atom with OCH₃ as a leaving group. - According to our view this is an intramolecular electrophilic amination [16] (O-methyl-hydroxylamine is a reagent for (intermolecular) electrophilic aminations).
Having these data in mind, a base catalyzed formation of our 1H-aziridines from 3-hydroxyamino-1,3-diphenylpropan-1-ones by the attack of C-2-carbanion at the N-atom with HO⁻ as the leaving group is conceivable.

To the best of our knowledge this is the first case of aziridine formation with the intermediacy of 1,3-diaryl-3-hydroxyamino-1-propanones and with OH⁻ as a leaving group in the ring closure.

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Experimental Part

General remarks: Lit. 5.

1-(2,6-Dichloro-4-methoxyphenyl)ethan-1-ol

To a Grignard reagent from 4.26 g (30 mmole) CH₃I and 0.73 g (30 mmole) Mg in 15 ml of absol. Et₂O are added dropwise 2.05 g (10 mmole) 2,6-dichloro-4-methoxybenzaldehyde (6a) in 20 ml of absol. Et₂O and 20 ml of absol. THF at -5°C. After stirring for 1 h at room temp., 30 ml of satd. NH₄Cl-solution are slowly added with ice bath cooling. The org. solvents are evaporated in vacuo, the water phase is diluted with 30 ml of absol. THF and evaporated in vacuo. The residue is purified (SiO₂-Celite and benzene). Benzene is evaporated in vacuo, the aziridines are eluated by EtOAc and the corresponding acetophenone 7 at room temp. Stirring is continued for 12 h. Then the org. phase is separated, diluted with 200 ml of CH₂Cl₂, washed with water and satd. NaCl-solution, dried (Na₂SO₄) and evaporated in vacuo.

trans-1,3-Bis-(2,6-dichloro-4-methoxyphenyl)-2-propan-1-ones (1a, 1b)

Yield 94%, m.p. 122 - 123°C (absol. EtOH). - C₁₇H₁₂Cl₂O₄ (406.1) Calcd. C 50.3 H 2.98 Found C 50.4 H 3.01. - CW-IR (KBr): υ = 3090, 3010 cm⁻¹ (CH aromat.); 2980, 2940, 2890 (CH aliph.); 2845 (OCH₃); 1660 (C=O); 1635, 1595 (C=C). - ¹H-NMR (CDCl₃): δ (ppm) = 7.46 (d; J = 16.5 Hz, 1H, =CH), 7.08 (d; J = 16.5 Hz, 1H, =CH), 6.92 (s; 4H, aromat.), 3.83, 3.80 (2s; 6H, OCH₃).

trans-1,3-Bis-(2,6-dichloro-4-methoxyphenyl)-2-propan-1-one (1b)

Yield 95%, m.p. 122 - 124°C (absol. EtOH). - C₁₇H₁₂Cl₂O₄ (406.1) Calcd. C 50.3 H 2.98 Found C 50.3 H 3.12. - CW-IR (KBr): υ = 3010 cm⁻¹ (CH aromat.); 2980, 2940 (CH aliph.); 2840 (OCH₃); 1660 (C=O); 1630, 1565 (C=C). - ¹H-NMR (CDCl₃): δ (ppm) = 7.41 (d; J = 16.5 Hz, 1H, =CH), 7.35 - 6.84 (m; 4H aromat.), 6.88 (d; J = 16.5 Hz, 1H, =CH), 3.92, 3.89 (2s; 6H, OCH₃).

2-Benzoyl-3-phenyl-1H-aziridines (4a, 4b)

At 50°C 18.3 g (0.263 mole) of hydroxylamine-HCl in 40 ml of water are added drop by drop to a solution of 0.1 mole in 240 ml of EtOH, followed by dropwise addition of 24 g (0.428 mole) KOH in 40 ml of water. After boiling for 20 min, the mixture is evaporated to dryness in vacuo. After addition of 1.5 L of water stirring is continued for 1 h. The precipitate is filtered off, dried over night in vacuo and purified by CC (SiO₂): impurities are removed by CH₂Cl₂, the aziridines are eluted by EtOAc and crystallized from 96% EtOH: faint yellow crystals.

trans-2-(6-Dichloro-4-methoxybenzyl)-3-(2,6-dichloro-4-methoxyphenyl)-1H-aziridine (4a)

From 1a: yield 51%; m.p. 111 - 112°C. - C₁₇H₁₂Cl₂NO₃ (421.1) Calcd. C 48.5 H 3.11 N 3.33 Found C 48.5 H 3.11 N 3.00. - CW-IR (KBr): υ = 3291, 3258 cm⁻¹ (NH); 3087, 3010 (CH aromat.); 2975, 2948 (CH aliph.); 2842 (OCH₃); 1697 (C=O); 1597 (C=C). - ¹H-NMR (CDCl₃): δ (ppm) = 6.90 (s; 9H, aromat.) 6.83 (s; 2H aromat.), 3.77 (s; 3H, OCH₃), 3.48 (dd; J = 3.0 Hz, 3JHCH = 9.0 Hz, 1H, CH; H/D exh.: d; J = 3.0 Hz), 3.28 (dd; J = 3.0 Hz, 3JHCH = 9.0 Hz, 1H, CH; H/D exh.: d; J = 3.0 Hz), 2.62 (t; 3JHCH = 9.0 Hz, 1H, NH exh.). - ¹³C-NMR (CDCl₃): δ (ppm/62.5µM) = 199.2 (C-1), 160.9 (C-4') aromat., 159.5 (C-4'') aromat., 136.8, 132.3, 130.4, 125.1, 114.4 aromat., 114.3 (C-H aromat.), 55.9 (OCH₃), 55.7 (OCH₃), 46.3 (C-2), 41.1 (C-3). These data are in accordance with those published by Cromwell 18 for benzoyl-phenyl-aziridines. - EI-MS: m/z (%) = 419 (M⁺, Cl⁻), 384 (43; (M - Cl⁻), ortho-effect); 356 (7; (384 - CO₂)); 348 (8; 384 - HCl); 216 (25; (Ar-CH(NH)CH₃)); 203 (100; (Ar-CO⁺)); 189 (44; (Ar-CHO⁺)). The formation of Ar-CH₂⁺ in phenylaziridines by rearrangement is discussed by Searles 19 and Weber 20.

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trans-2-[2,6-Dichloro-3-methoxybenzoyl]-3-(2,6-dichloro-3-methoxyphenyl)-aziridine (4b)

From 1b, yield 55%; m.p. 117 - 118°C. - C_{2}H_{3}Cl_{2}NO (421.1) Calcd. C 48.5 H 3.11 N 3.3 Found C 48.6 H 3.09 N 3.3. - FT-IR (KBr): ν = 3291, 3258 cm⁻¹ (NH); 3087, 3010 (CH aromat.); 2975, 2948 (CH aliph.); 2842 (CH=; 1697 (C=O); 1597 (C=C). - 1H-NMR (CDCl₃): δ (ppm) = 7.33 (d; J = 9.0 Hz, 1H aromat.), 7.21 (d; J = 9.0 Hz, 1H aromat.), 6.94 (d; J = 9.0 Hz, 1H aromat.), 6.82 (d; J = 9.0 Hz, 1H aromat.), 3.93 (s; 3H, OCH₃), 3.86 (s; 3H, OCH₃). - C-NMR (CDCl₃): δ (ppm) = 46.2 (C-2), 41.6 (C-3). - Mass: m/z (%) = 419 (7, [Cl⁻]+); 384 (44; [M - Cl]⁻, ortho-effect); 356 (9; [M - Cl - CO]⁻); 248 (8; M - Cl - HCl)⁺; 216 (32; [Ar-CH(NH)(CH₃)]⁺); 203 (93; [Ar-CD₂]+); 189 (100; [Ar-CH₃]+).

References