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Unexpected Hydrogenation of C–C-Double Bonds with *tert*-Butyl Iodide [1])

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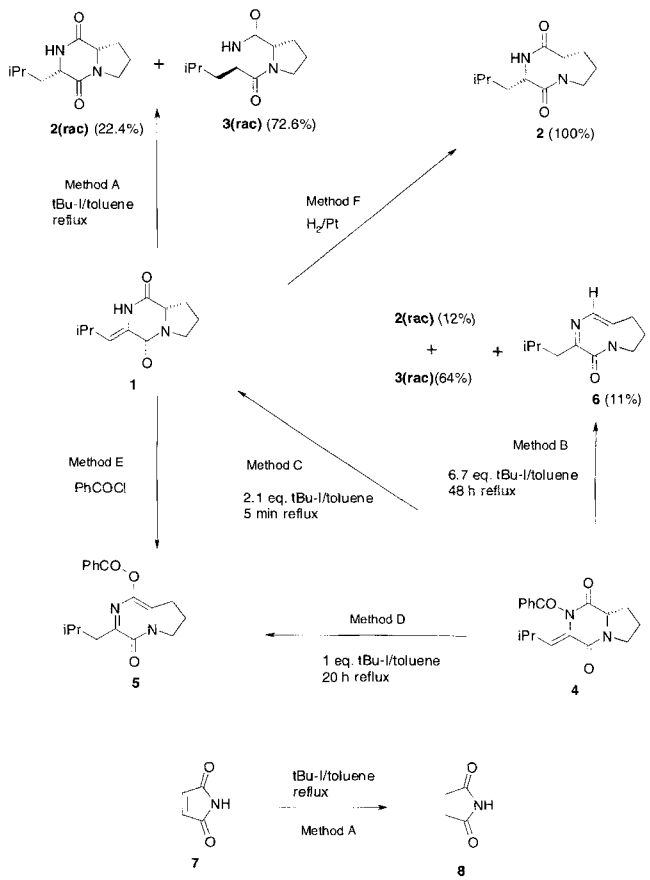
Abstract. Heating of 3-isobutylidene-2,5-diketopiperazines **1** or **4**, maleinimide or 2,3-dichloro-5,6-dicyano-*p*-benzoquinone with *tert*-butyl iodide in toluene gave rise to hydrogenation of the conjugated C–C-double bond affording 3-isobutyldiketopiperazines **2**(***rac***) and **3**(***rac***), succinimide, or 2,3-dichloro-5,6-dicyanohydroquinone, respectively. Furthermore, an interesting N–O-migration of a benzoyl group as well as reductive aromatization to pyrazines **5** and **6**, respectively, were observed.

Stereoselective addition reactions (catalytic hydrogenation [1, 2], epoxidation [3], addition of diazomethane [4]) to the C–C-double bond of 3-ylidene-2,5-diketopiperazines, such as **1** or **4**, have been used in the synthesis of interesting α-aminoacid derivatives. Recently the radical addition of an alkyl group by alkylmercury compounds in the presence of $NaBH_4$ to 3-methylidene-2,5-diketopiperazine was reported generating one new stereogenic centre [5]. We attempted an analogous radical addition to the (*S*)-isobutylidene-2,5-diketopiperazines **1** and **4** using alkyl halides in the presence of tributyltinhydride and AIBN in order to generate two stereogenic centres. Unfortunately no C–C-bond formation could be accomplished. Just unchanged starting material was recovered in most cases. Obviously the higher degree of substitution of the C–C-double bond lowers the reactivity of **1** and **4** as compared with corresponding 3-methylidene-2,5-diketopiperazines. While using *tert*-butyl iodide in the presence of Bu_3SnH/AIBN however a reaction was observed with the isobutylidene-2,5-diketopiperazine **1**. But the product obtained was no alkylation product but a diastereomeric mixture of racemic 3-isobutyl-2,5-diketopiperazines **2**(***rac***) and **3**(***rac***). The same mixture was also obtained in high yield (95%) when the solution of **1** in toluene was refluxed just in the presence of *tert*-butyl iodide (Method A). Obviously, *tert*-butyl iodide served as hydrogenation reagent. The stereoselectivity of this hydrogenation (preferred α-attack affording **3**(***rac***) as major product, **2**(***rac***) : **3**(***rac***) = 10 : 32) is opposite to the known catalytic hydrogenations of 3-alkylidene-2,5-diketopiperazines, where exclusive β-attack was observed [1, 2]. In order to prove the relative configuration of racemic *cis*-compounds **2**(***rac***) and racemic *trans* **3**(***rac***) we synthesized optically active *cis*-compound **2** by catalytic hydrogenation (Method F) of the isobutylidene-2,5-diketopiperazines **1** in this stereochemically unambigious way. The *cis*-product **2**(***rac***) and the optically active **2** (obtained by Method F) showed identical NMR spectra while those of the *trans*-compound **3**(***rac***) and **2** were different. (*S,S*)-Isobutyl-2,5-diketopiperazine **2** is a known natural product

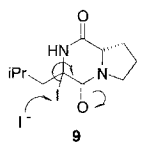


1) Presented in part at the third conference on iminium salts, Stimpfach-Rechenberg (Germany), September 17–19, 1997

(for ex-amples see reference [6]). **2** (*e.g.* reference [7, 8]) and its enantiomer (*e.g.* reference [9]) and enantiomerically pure *trans*-compounds **3** (*e.g.* reference [10]) have been repeatedly synthesized by cyclization of di or tripeptides of proline and leucine or starting from ergot-alkaloids.

Further investigations revealed that the *N*-benzoyl-3-isobutylidene-2,5-diketopiperazine **4** could also be hydrogenated to the isobutyldiketopiperazines **2** (12%) and **3** (64%) with *tert*-butyl iodide (Method B). But in addition the isobutyl-2,4-diazinone **6** was obtained in 11% yield. Reactions of lower excess or equimolar quantities of the benzoyl-3-isobutylidene-2,5-diketopiperazine **4** and *tert*-butyl iodide gave rise to the debenzoylated product **1** (Method C) or the rearranged 5-benzoyloxy-pyrazine-2-one **5** (Method D), respectively also depending on the duration of reflux (5 min or 20 h, respectively). *tert*-Butyl iodide could further be used (Method A) to hydrogenate maleinimide or 2,3-dichloro-5,6-dicyano-*p*-benzoquinone (DDQ) but left maleic anhydride, butenolide and stilbene unchanged. Under the same conditions complex mixtures were obtained with cinnamic aldehyde, diphenylcyclopropenone while acrylamide afforded 3-iodopropanamide. Finally pyrrolidinocyclohexene gave just the corresponding iminium salt after heating with *tert*-butyl iodide in toluene.

The unusual function of *tert*-butyl iodide as hydrogenating reagent is probably caused by its known thermal elimination [11] giving isobutene and HI. The hydrogen iodide formed acts as hydrogen donor generating iodine as by-product which was found in the reaction mixture. HI has been used as hydrogenating reagent for 1,2-diacylalkenes [12] and 3,6-bisylidene-2,5-diketopiperazine [13] before. But just one out of the two C–C-double bond was hydrogenated in the latter case. As proposed in these known cases the hydrogenation itself is probably a multi-step process, i. e. primary addition of hydrogen iodide to the C–C-double bond (formation of **9** and **10**) and reductive C–I bond cleavage at the α-iodocarbonyl moiety by iodide ion generating iodine and an enolate which is finally protonated. These models can also explain why normal α,β-unsaturated carbonyl compounds lacking a second carbonyl group or an enamine moiety and thus do not give α-iodo-carbonyl intermediates or mere enamines were not hydrogenated with *tert*-butyl iodide.



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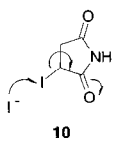

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The observed debenzoylation of **4** in the presence of *tert*-butyl iodide is presumably also caused by eliminated hydrogen iodide affording **1** and benzoyl iodide. After longer reaction times these two products react with each other by *O*-benzoylation and proton shift thus affording the 5-benzoyloxy-pyrazine-2-one **5**. Further evidence for this mechanism was found by the successful attempt to transform the 3-isobutylidene-2,5-diketopiperazine **1** to the benzoyloxypyrazinone **5** by means of benzoyl chloride (Method E) affording racemic **1** and **4** as by-products. Usually substituents at *N*-heterocycles migrate from the exocyclic *O*-position to the ring nitrogen atom rather than the other way round. But in the case of the transformation of the *N*-benzoylpiperazindione **4** to the *O*-benzoylpyrazine **5** this unusual migration is driven by aromatization. The phenomenon of racemization in all reactions but method F is due to the high temperature applied. Product **6** formed from **4** in the presence of excess of *tert*-butyl iodide after long reaction times could eventually derive from **5** by HI-hydrogenation of the C=C-double bond and final elimination of benzoic acid.

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Experimental

General. ^{1}H NMR and ^{13}C NMR spectra were recorded at 300 and 75.5 MHz respectively on a BRUKER AC-300 with TMS as internal standard. Mass spectra (HP 5995 A) were measured at 70eV. Kieselgel, mesh size 0.4–0.6 mm (MERCK), was used for preparative chromatography. Starting materials **1** and **4** were prepared following known procedures [2] from hippuric acid, isobutyraldehyde and L-proline. Maleinimide and DDQ were purchased from ALDRICH.

Hydrogenation of 3-Isobutylidene-2,5-diketopiperazine (1), Maleinimide and 2,3-Dichloro-5,6-dicyano-*p*-benzoquinone with *tert*-Butyl Iodide

Method A: *t*-Bu–I (0.5 mL, 4.2 mmol) was added to a mixture of the 3-isobutyliden-2,5-diketopiperazine **1** (208 mg, 1 mmol), maleinimide (97 mg, 1 mmol) or 2,3-dichloro-5,6-dicyano-*p*-benzoquinone (227 mg, 1 mmol) and dry toluene (10 mL). The mixture was refluxed under argon for 5h. After evaporation *in vacuo* the remaining material was submitted to flash chromatography on silica gel (acetone/$CHCl_3$ = 1:2) or was recrystallized from ethanol/water under argon in case of 2,4-dichloro-5,6-dicyanohydroquinone.

cis-3-Isobutyl-hexahydropyrrolo[1,2-a]pyrazine-1,4-dione **2**(***rac***)

Colourless crystals (22.4%). *m. p.* 150–152 °C, R_f = 0.29. – ^{1}H NMR ($CDCl_3$): δ/ppm = 0.90 (quart., J = 6.6 Hz, 6H, $2CH_3$), 1.71–2.29 (m, 7 H, $3CH_2$, C<u>H</u>Me_2), 3.55 (m, 2H, NCH_2), 3.94 (dd, J=3.5, J=9.3, 1H, NC<u>H</u>-*i*-Bu), 4.05 (t, J=8.0 Hz, 1H, NC<u>H</u>-5-ring), 6.70 (s, 1H, NH). – ^{13}C NMR ($CDCl_3$): δ/ppm = 21.7 CH_3, 23.6 CH_3, 23.1 CH_2<u>C</u>H_2CH_2, 24.9 <u>C</u>HMe_2, 28.4 <u>C</u>H_2CHN5-ring, 38.9 <u>C</u>H_2CHMe_2, 45.8 CH_2N-5-ring, 53.8 CHN-6-ring, 59.3 CH-5-ring, 166.7 CO, 171.0 CO. – IR (KBr): ν/cm^{-1} = 3258 (NH), 1658 (C=O), 1669 (C=O). – MS, *m/z* (%): 211 (M^++1, 0.8), 210 (M^+, 0.14), 164 (68), 70 (100).

$C_{11}H_{18}N_2O_2$	calcd.:	C 62.83	H 8.63	N 13.32
(210.3)	found:	C 62.99	H 8.11	N 13.31.

trans-3-Isobutyl-hexahydropyrrolo[1,2-a]pyrazine-1,4-dione **3**(***rac***)

Colourless crystals (72.6%). *m.p.* 100–102 °C, R_f = 0.24. – ^{1}H NMR ($CDCl_3$): δ/ppm = 0.89 (d, J = 7.0 Hz, 6H, $2CH_3$), 1.53–2.33 (m, 7H, $3CH_2$, C<u>H</u>Me_2), 3.42–3.59 (m, 2H, NCH_2), 3.84–3.93 (m, 1H, NC<u>H</u>-*i*-Bu), 4.01 (dd, J=8.8 Hz, J=2.3 Hz, 1H, NC<u>H</u>-5-ring), 7.84 (s, 1H, NH). – ^{13}C NMR ($CDCl_3$): δ/ppm = 21.8 CH_3, 23.4 CH_3, 22.6 CH_2<u>C</u>H_2CH_2,

24.7 $\underline{C}HMe_2$, 29.3 $\underline{C}H_2CHN5$-ring, 42.9 $\underline{C}H_2CHMe_2$, 45.9 CH_2N-5-ring, 56.5 CHN-6-ring, 58.4 CH-5-ring, 167.0 CO, 170.3 CO. – IR (KBr): ν/cm^{-1} = 3200 (NH), 1682 (C=O), 1653 (C=O). – MS, *m/z* (%): 211 (M^++1, 0.5), 210 (M^+, 0.1), 154 (62), 70 (100).

$C_{11}H_{18}N_2O_2$	calcd.:	C 62.83	H 8.63	N 13.32
(210.3)	found:	C 62.61	H 8.33	N 13.34.

Succinimide (**8**)

Quantitative yield, *m. p.* 123–125 °C (ref. *m.p.* 123–125 °C [14])

2,3-Dichloro-4,5-dicyanohydroquinone

Yield 92%, *m.p.* 260–262 °C (ethanol/water) (ref. *m.p.* 265 °C [15])

Reaction of 4-Benzoyl-3-isobutylidene-2,5-diketopiperazine 4 with *tert*-Butyl Iodide

Method B: *t*-Butyl iodide (0.8 mL, 6.7 mmol) was added to a mixture of the *N*-benzoyl-3-isobutylidendiketopiperazine **4** (312 mg, 1 mmol) and dry toluene (10 mL). The mixture was refluxed under argon for 2d. After evaporation *in vacuo* the remaining material was dissolved in acetone (5 ml) and stirred with saturated aqueous KF at room temperature for 2 days. The mixture was extracted with $CHCl_3$ (3×20 mL). After drying with Na_2SO_4 the solvent was evaporated *in vacuo* and the remainder was finally submitted to flash chromatography on silica gel (acetone/$CHCl_3$ 1:2) affording **2** (12%), **3** (64.3%) and **6** (11%)

1-Benzoyloxy-3-isobutyl-7,8-dihydro-6H-pyrrolo[1,2-a] pyrazine-4-one (**6**)

Colourless solid, R_f = 0.35. – ^{1}H NMR ($CDCl_3$): δ/ppm = 0.89 (d, J = 6.6 Hz, 6H, $2CH_3$), 2.15 (m, 3H, $CH_2C\underline{H}_2CH_2$, $C\underline{H}Me_2$), 2.63 (d, *J* = 7.2 Hz, 2H, $C\underline{H}_2CH$), 3.02 (t, *J* = 7.7 Hz, 2H, CH_2–C=C), 4.06 (t, *J* = 7.3 Hz, 2H, NCH_2), 7.22 (s, 1H, =CH). – ^{13}C NMR ($CDCl_3$): δ/ppm = 21.9 $CH_2\underline{C}H_2CH_2$, 23.0 $2CH_3$, 27.2 $\underline{C}HMe_2$, 29.8 =C–$\underline{C}H_2$, 41.9 $\underline{C}H_2CHMe_2$, 49.0 CH_2N, 118.6 H$\underline{C}$=C, 140.6 HC=$\underline{C}$, 156 C=N, 157 C=O.

Method C: Following method B by using only 2.1 mmol of *t*-butyl iodide and refluxing for just 5 min. afforded isobutylidene-hexahydropyrrolo[1,2-a]pyrazine-2,4-dione **1**, yield after flash chromatography (R_f = 0.39, R_f of starting material **4** = 0.54) 17.8%, *m.p.* 168–170 °C (ref. *m.p.* 168–170 °C [2]), $[\alpha]_D^{20}$ = + 28.0 (c = 1.85 $CHCl_3$).

Method D: Following method B by using only 1 mmol of *t*-butyl iodide and refluxing for 20h afforded 1-benzoyloxy-3-isobutyl-7,8-dihydro-6H-pyrrolo[1,2-a]pyrazine-4-one **5** in 90% yield after flash chromatography (EtOAc/hexane 9:1, R_f = 0.46, by-products **1** R_f = 0.30 and **4** *R* = 0.54). Colourless amorphous solid, *m.p.* 90–96 °C. – ^{1}H NMR ($CDCl_3$): δ/ppm = 0.88 (d, *J* = 6.7 Hz, 6H, $2CH_3$), 2.12–2.23 (m, 3H, $CH_2C\underline{H}_2CH_2$, $C\underline{H}Me_2$), 2.61 (d, *J* = 7.2 Hz, $C\underline{H}_2$–CH), 2.96 (t, *J* = 7.7, 2H, $C\underline{H}_2$–C=), 4.11 (t, *J* = 7.4 Hz, 2H, NCH_2), 7.42 (m, 2H, arom), 7.54–7.59 (m, 1H, arom), 8.10 (m, 2H, arom). – ^{13}C NMR ($CDCl_3$): δ/ppm = 23.0 $2CH_3$, 21.7 $CH_2\underline{C}H_2CH_2$ 27.2 ($\underline{C}HMe_2$), 29.0 $\underline{C}H_2C$=, 41.6 $\underline{C}H_2CHMe_2$, 49.8 CH_2N, 128.9 N–C=, 129.0 CH_{arom}, 130.7 CH_{arom}, 132.1 C_{arom}, 134.4 CH_{arom}, 155.4 C=N, 155.9 CO, 164.9 CO. – MS, *m/z* (%): 313 (M^++1, 1), 312 (M^+, 4), 207 (8), 106 (8), 105 (100).

$C_{18}H_{20}N_2O_3$	calcd.:	C 69.21	H 6.45	N 8.97
(312.4)	found:	C 69.33	H 6.45	N 9.00.

Reaction of 3-Isobutylidene-2,5-diketopiperazine 1 with Benzoyl Chloride

Method E: A solution of 3-isobutylidene-2,5-diketopiperazine **1** (208 mg, 1 mmol) and benzoyl chloride (127 µL, 1.1 mmol) in dry toluene (8 mL) was refluxed under argon for 44 h. After evaporation to dryness under vacuum the remaining material was submitted to flash chromatography (EtOAc/hexane = 9 : 1) affording racemic **1** (31%, R_f = 0.30), racemic *N*-benzoyl-3-isobutylidene-2,5-diketopiperazine **4** (19%, R_f = 0.54) and the 1-benzoyloxy-3-isobutyl-7,8-dihydro-6*H*-pyrrolo[1,2-*a*] pyrazine-4-one (**5**) (54%, R_f = 0.46).

Method F: A mixture of the 3-isobutylidene-2,5-diketopiperazine **1** (208 mg, 1 mmol), Pd/C (10%, 40 mg/Aldrich) and EtOH was kept under hydrogen at 1 atm at room temperature for 17 h. After filtration through Celite 545 the filtrate was evaporated *in vacuo*. The remainder was submitted to column chromatography (acetone/$CHCl_3$ = 1: 2) affording 0.21 g (100 %) of the (*S,S*)-isobutyl-2,5-diketopiperazine **2** as colourless crystals. *m.p.* 150–152 °C (AcOEt/hexane) (reference *m.p.* 151–153 [7]), $[\alpha]_D^{20}$ = –148.2 (*c* = 1.2, $CHCl_3$). The ^{1}H-NMR and the ^{13}C NMR spectra were identical with the spectra of the racemate **2**(***rac***).

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