Electron Impact Induced Loss of C-5/C-8 Substituents of 1,2,3,4-Tetrahydroisoquinolines, V:

Synthesis and Mass Spectrometric Fragmentation of Dihydroisoindole Derivatives*)

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C-8-substituted N-methyl-1,2,3,4-tetrahydroisoquinoline radical cations lose the complete substituent in a one step reaction giving rise to an unexpected ion at m/z 146, which is probably identical with the dihydroisoindolylmethyl-cation **A**. The dihydroisoindoles **1**, **10**, and **16** were prepared as potentially alternative precursors of ion **A**. However, the ion at m/z 146 in their EI mass spectra is of very low intensity, so CID-experiments for structural comparison could not be performed. The electron impact induced fragmentations of **1**, **10**, and **16** are discussed.

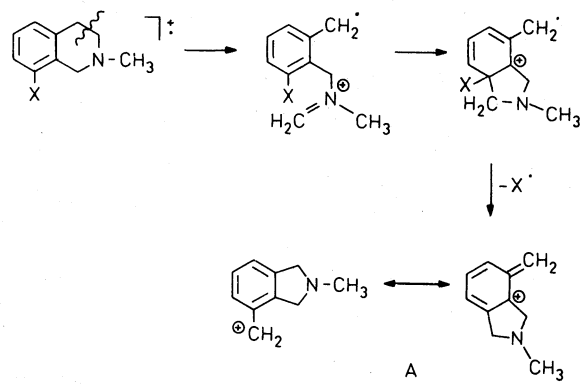
Elektronenstoß-induzierter Verlust der Substituenten an C-5 und C-8 bei 1,2,3,4-Tetrahydroisochinolinen, 5. Mitt.:
Synthese und massenspektrometrische Fragmentierungen von Dihydroisoindol-Derivaten

An C-8 substituierte N-Methyl-1,2,3,4-tetrahydroisochinolin-Radikalkationen verlieren den gesamten Substituenten in einstufiger Reaktion unter Bildung eines unerwarteten Ions bei m/z 146, dessen postulierte Identität mit dem Dihydroisoindolylmethyl-Kation **A** geprüft werden sollte. Die Dihydroisoindole **1**, **10** und **16** - mögliche Vorläufer von **A** - wurden synthetisiert. In ihren EI-MS tritt das Ion bei m/z 146 mit nur sehr geringer Intensität auf, CID-Messungen zum Strukturvergleich konnten daher nicht durchgeführt werden. Die Elektronenstoß-induzierten Fragmentierungen von **1**, **10** und **16** werden diskutiert.

N-Methyl-1,2,3,4-tetrahydroisoquinolines substituted at C-5 and/or C-8 lose these substituents upon electron impact (EI) induced ionization forming fragment ions of high intensity which correspond to a formally "simple" cleavage of the C_{Ar}-X-bond. If X is a carbon chain these ions can be more prominent than ions resulting from benzylic cleavage[1].

This unexpected behaviour points towards functional group interaction in the $M^{+\cdot}$ prior to bond breaking, an assumption supported by the fact that the percentage of the total ion current corresponding to the $(M\text{-}X)^+$-ions is increased by reducing the electron energy from 70 eV to 10 eV. These results are typical of rearrangements preceding fragmentation and are in contrast to simple bond rupture[2,3]. Therefore, we proposed that dihydroisoindolylmethyl cations might be formed from C-8-substituted N-methyl-1,2,3,4-tetrahydroisoquinolines under EI conditions (Scheme 1):

In order to verify this hypothesis by CID-MIKES+) we synthesized C-4-substituted dihydroisoindoline derivatives as precursors which are expected to form ion **A** by a favoured cleavage after EI. Here we describe the synthesis of some pertinent molecules.



Scheme 1

1) 4-(N-Benzoyl-aminomethyl)-2,3-dihydro-2-methyl-1H-isoindole (1)

This compound is supposed to form ion **A** by benzylic cleavage (Scheme 2):

+) Collision Induced Dissociation - Mass Analyzed Ion Kinetic Energy Spectroscopy[3].

* Part IV: see lit.[1].

** Taken in part from F. Knefeli, Ph. D. Thesis Regensburg 1987; Arch. Pharm. (Weinheim) *321*, 656 (1988).

*** Herrn Prof. Dr. H. J. Roth, Tübingen, zum 60. Geburtstag gewidmet.

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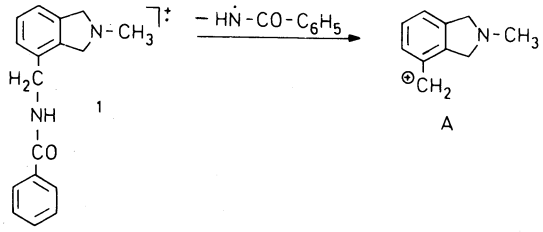
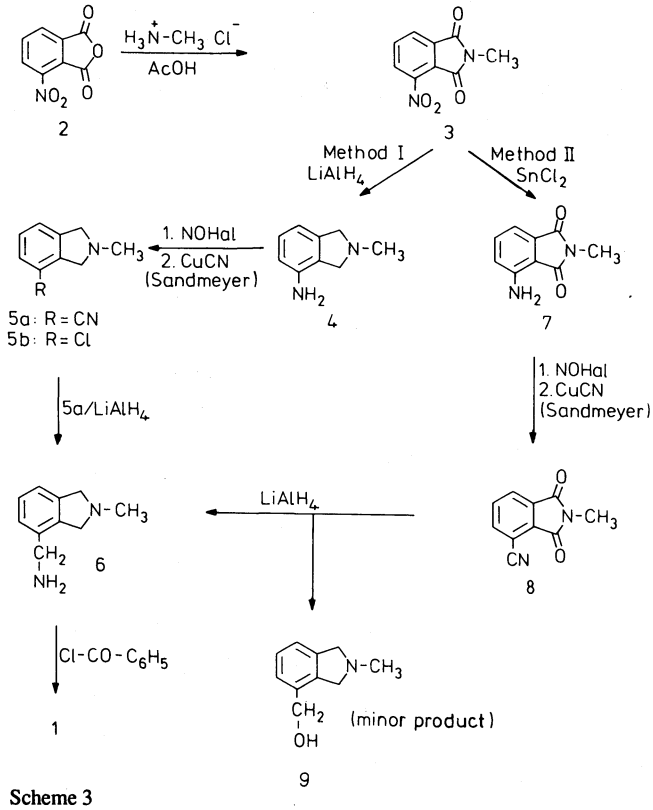


Scheme 2

1 was prepared on two routes:

Method I

(Substituted) phthalic anhydrides react with methylamine to the corresponding N-methylphthalimides[4]. Subsequent reduction with $LiAlH_4$ leads to 2,3-dihydro-2-methyl-1H-isoindoles[5] (Scheme 3):



Scheme 3

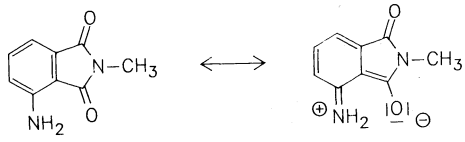
The nitrophthalimide **3**, prepared from **2** according to *Williams*[6] in 73% yield, was reduced to **4** with 1 mole of $LiAlH_4$. **4** is very labile; freshly distilled material decomposes rapidly. Therefore, **4** was processed directly to **5a** in a *Sandmeyer* reaction.

All efforts to purify **5a** failed: the mass spectrum showed additional molecular ions at m/z 165 and m/z 167 to which was attributed structure **5b** on account of the isotope pattern and the loss of 35/37 mu ($Cl^{\cdot}$) from $M^{+\cdot}$.

5a was reduced to **6** by $LiAlH_4$ and benzoylated to the amide **1**. For ms data see section "Mass spectra".

Method II

On account of the lability of **4** mentioned above we tried to optimize the synthesis of **1** by $SnCl_2$-reduction of **3** to **7**[7]. **7** is a very weak base (phenylogous amide): even washing of the crude white hydrochloride with water liberated the yellow base (λmax = 387 nm):



Scheme 4

Because of its low basicity **7** had to be diazotised in suspension. So the yields of the cyano phthalimide **8** are low. **8** is colourless (λmax = 281 nm) as expected. Its $M^{+\cdot}$ loses CO_2 (see "Mass Spectra"). **8** was reduced with $LiAlH_4$ in a one pot reaction affording the aminomethyl derivative **6** as expected besides traces of the hydroxymethyl-dihydroisoindole **9**. The structure of **9** was confirmed by independent synthesis (vide infra).

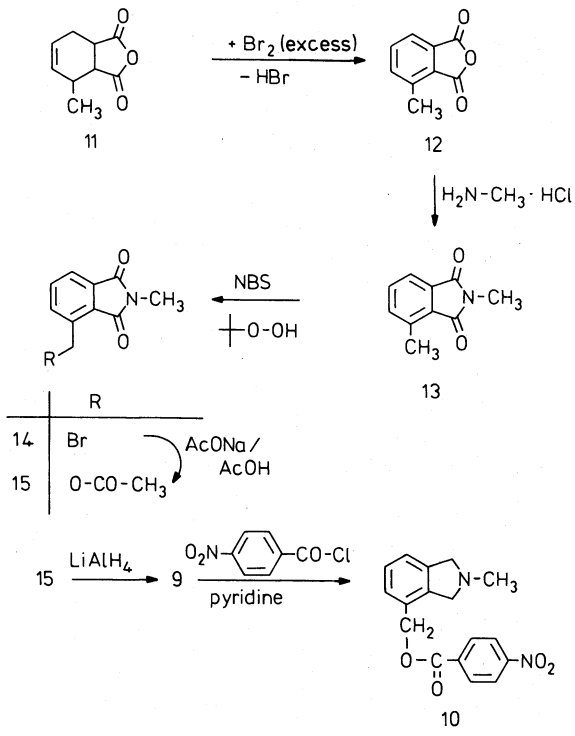
We have no clear-cut explanation for the formation of **9**. The considerations of *Brown* and *Garg*[8] might give a hint for a correct interpretation, albeit the origin of the side chain oxygen from water during work-up was excluded. **6** was benzoylated conventionally to the amide **1** which proved to be unsuitable as a precursor for ion **A**: the dominant peak is at m/z 145 instead of m/z 146 (see "Mass Spectra").

Under EI-MS conditions benzyl benzoates form benzyl and benzoyl cations with high rel. intensities[9]. Therefore, we expected the p-nitrobenzoate **10** to be a suitable precursor of ion **A**.

2) 3-Dihydro-2-methyl-4-(4-nitrobenzoyloxymethyl)-1H-isoindole (10)

As starting material for the synthesis of **10** we used the methyl-tetrahydrophthalic anhydride **11**[10], prepared from 1,3-pentadiene and maleic anhydride. In our hands the best method for aromatization to **12** proved to be addition of Br_2 with subsequent elimination of HBr according to *Newman*[11] (Scheme 5):

Treatment of **12** with methylamine-HCl as described above afforded the phthalimide **13** which we tried to deprotonate at the methyl group in order to react the resultant carbanion with convenient electrophiles. However, even treatment with lithium diisopropylamide did not work properly as indicated by the low incorporation rate of deuterium after quenching with D_2O. Therefore, we functionalized the methyl moiety in **13** by bromination with N-bromosuccinimide/tert.-butylhydroperoxide leading to **14**, and exchanged Br by O-Ac giving **15**, which was reduced with $LiAlH_4$ to **9** in a one pot reaction. Consecutive esterification under *Einhorn*-conditions formed the p-nitrobenzoate **10**.



Scheme 5

Contrary to our anticipation in the ms of **10**, too, the ion at m/z 146 (ion **A**) was too small for CID-measurements (<5% rel. int. after correction for the ^{13}C-satellite of the prominent ion at m/z 145).

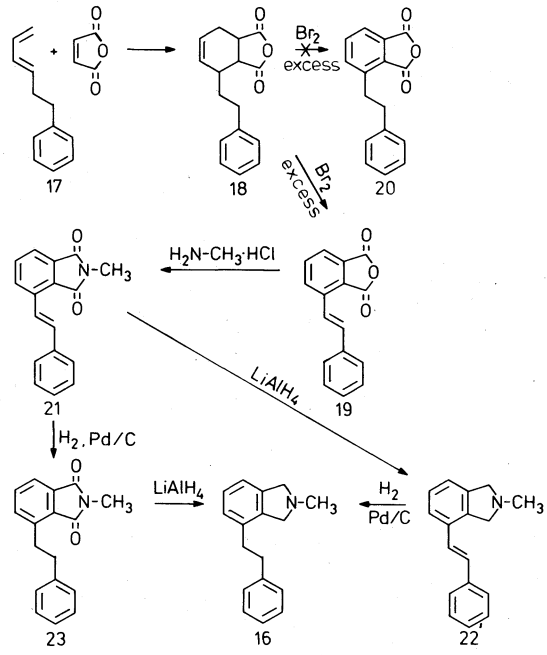
Obviously, the ion at m/z 145 is generated from **1** and **10**, respectively, by transfer of one H of the methylen group in position 1 to the side chain heteroatoms, (see "Mass Spectra"). We intended to avoid this process by introducing a bisbenzylic side chain which is expected to give rise to favourable benzyl cations (or radicals) after ionization.

3) 2,3-Dihydro-2-methyl-4-(2-phenylethyl)-1H-isoindole (16)

The preparation of 1,2,3,6-tetrahydro-3-(2-phenylethyl)-phthalic anhydride (**18**) by *Diels-Alder*-reaction of 6-phenyl-1,3-hexadiene (**17**) and maleic anhydride was described[12]. So we varied the route of Scheme 5, as depicted in Scheme 6:

The diene **17** is prepared by dehydration of 6-phenyl-1-hexene-3-ol[12] with $KHSO_4$ in 10 - 15% yield. Our variation of this process (see Experimental Part) afforded **17** in 67% yield.

When we aromatized **18** analogously to **11** we found that additional dehydrogenation in the side chain hat occurred leading to the faintly yellow stilbene **19**. As *Cohen*[12] had obtained the desired compound **20** by Se-dehydrogenation of **18** only in low yields (10 - 15%), we went on with the stilbene **19** and hydrogenated the side chain double bond at a later stage. So, **19** was converted to the phthalimide **21** (as described for **12** to **13**) which was reduced to **22** and hydrogenated to the target molecule **16**.



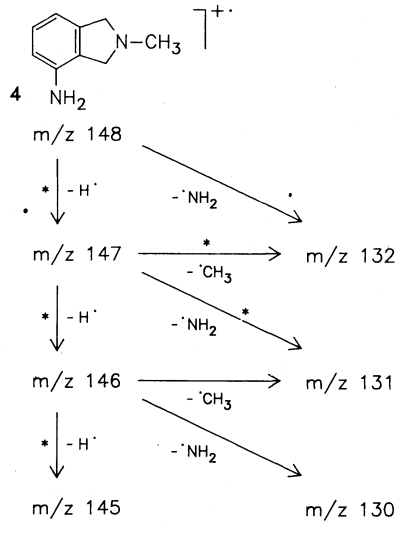
Scheme 6

Alternatively, **21** was hydrogenated to the dihydroisoindole derivative **23** which was reduced to **16**.

Unfortunately, the $M^{+\cdot}$ of **16** did not decompose by electron impact as expected; here, too, the ion at m/z 145 is dominant (see "Mass Spectra").

Mass Spectra

The mass spectrum (70 eV) of 4-amino-2,3-dihydro-2-methyl-1H-isoindole (**4**) is characterized by the base peak at m/z 147 $(M\text{-}H^{\cdot})^+$ which loses two additional H-atoms to m/z 146 and m/z 145, respectively (Scheme 7):



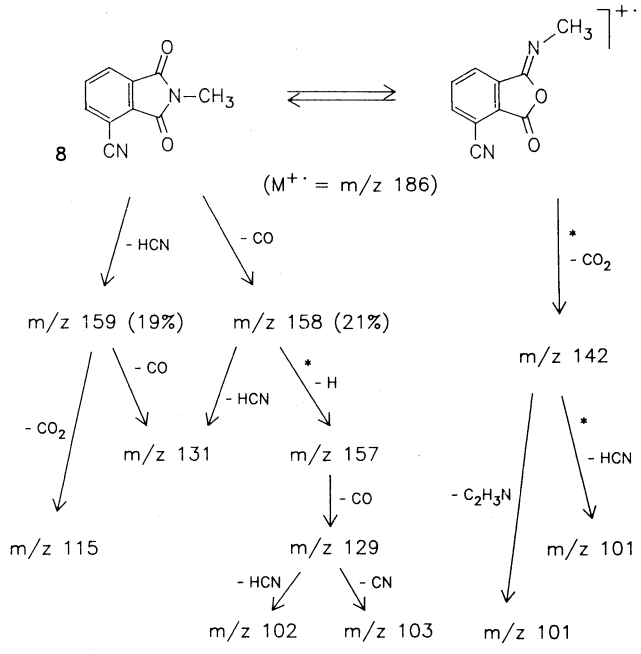
Scheme 7

High resolution (HR)-MS of the ion at m/z 132 (48% rel. int.) revealed a doublet: 75% of the signal correspond to $C_8H_8N_2$ $(M - H^{\cdot} - {}^{\cdot}CH_3)^+$, established by *118.53, the remaining 25% are represented by $C_9H_{10}N$ $(M - {}^{\cdot}NH_2)^+$. Analogously, the peak at m/z 131 (48% rel. int.) consists of 35%

$C_8H_7N_2$ (M - 2H - $\cdot CH_3$)$^+$ and 65% C_9H_9N (*116.74). On the other side the fragment at m/z 130 is homogeneous and results from m/z 146 by loss of $\cdot NH_2$.

The mass spectra of the aminomethyl-dihydroisoindole **6** and its N-benzoyl derivative **1** do not show molecular ions but very small (< 1%) (M - H)$^+$ - and (M - 2H)$^{+\cdot}$-peaks. Under CI-MS conditions (i-butane) (MH)$^+$ is the base peak in the ms of **1**. - The formation of m/z 145 - instead of ion **A** at m/z 146 - will be discussed in context with compounds **10** and **16**.

The mass spectrum (70 eV) of the cyanophthalimide **8** indicates a rearrangement of M$^{+\cdot}$ prior to fragmentation (Scheme 8):



Scheme 8

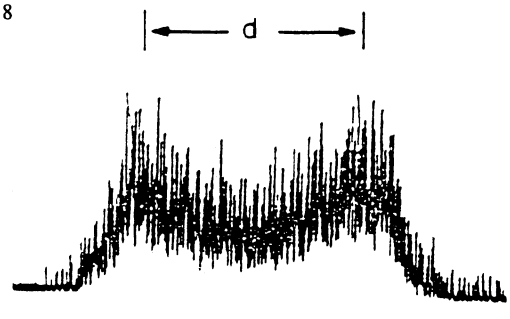


Fig. 1

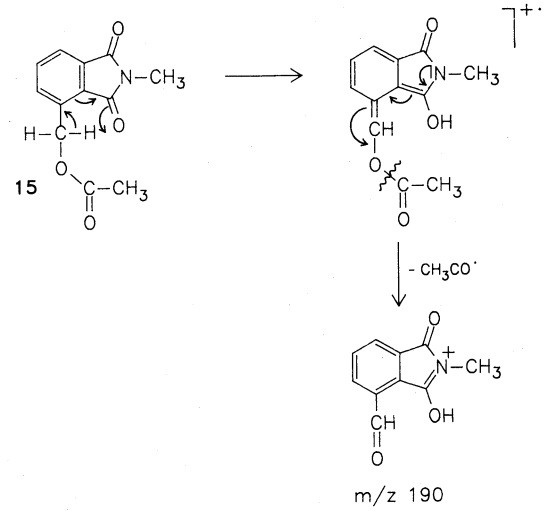
The ion at m/z 142 (66%; HR: $C_9H_6N_2$) is in accordance with (M - CO_2)$^{+\cdot}$. This assumption is corroborated by metastable ion analysis: B/E-linked scans of M$^{+\cdot}$ (m/z 186) indicate its correlation with m/z 142, B^2/E-linked scans show that m/z 142 originates directly from M$^{+\cdot}$. The wide dish-shaped peak[3] of M$^{+\cdot}$ in the B^2/E-linked scan spectrum (fig. 1) is characteristic for a relatively high amount of translational energy released in a unimolecular fragmentation. Metastable peaks of this shape are observed if a preceding isomerization is the rate determining step followed by fast dissoziation. Because the excited ion exists for a rather long time (10 ms) this process is called "slow dissociation"[13]. Loss of CO_2 from N-methyl- and N-phenyl-phthalimides is known[14], thermal rearrangements prior to ionization have been excluded[14,15].

At 10 eV M$^{+\cdot}$ of **9** (m/z 163) loses water to m/z 145 (60%; *143.01) by 1,4-elimination. The target ion at m/z 146 has <3% rel. intensity (corrected for the ^{13}C-satellite of m/z 145), at 70 eV it carries only <2% rel. intensity. The (M - H$\cdot$)$^+$-ion ejects 30 mu (CH_2O) to m/z 132 (43%; *107.56), followed by loss of a methyl radical to m/z 117 (16%; *103.70). - Contrary to our expectation the corresponding p-nitrobenzoyl ester **10** reveals a peak at m/z 146 of 5% rel. intensity (corrected for the ^{13}C-satellite of m/z 145) only, which is too low for CID-measurements. Loss of p-nitrobenzoic acid forms the base peak at m/z 145. This will be discussed in more detail (vide infra).

In the ms of the methylphthalimide **13** (M$^{+\cdot}$ = m/z 175, 100%) loss of CO_2 is prominent and explained analogously to that of **8**. The most intense fragment ion is at m/z 118; HR indicates C_8H_8N and C_8H_6O. It originates from m/z 146 which loses CO (*95.37) and from m/z 147 by loss of CH_3N. The precursor ion at m/z 146 arises from M$^{+\cdot}$ by a) loss of CH_3N (29 u) and b) by loss of CO (28 u), producing the ion at m/z 147 (10%; *123.48), which loses H$\cdot$ to m/z 146. Interaction of the carbonyl-oxygen with the CH_3-group in the peri-position causes H_2O-elimination from M$^{+\cdot}$ affording the ion at m/z 157 (1%; *140.85).

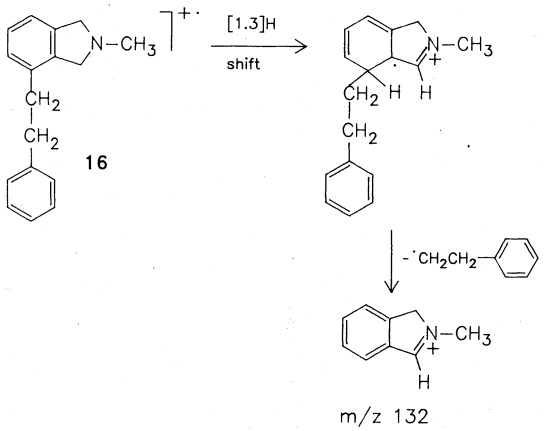
In the ms of the bromomethyl-phthalimide **14**, the fragment ion (M - $\cdot$Br)$^+$ gives rise to the base peak at m/z 174 even at nom. 12 eV. At 70 eV this ion loses HCN to m/z 147 (*124.19), which subsequently splits off CO to m/z 119.

The ms of the acetate **15** is surprising: M$^{+\cdot}$ is very low (2%) even at nom. 12 eV, CI-MS (i-butane) reveales (MH)$^+$ at m/z 234. Interestingly, the base peak at m/z 190 is formed by loss of CH_3-CO$\cdot$ instead of CH_3-COO$\cdot$ (m/z 174 has only 5% rel. int.), whereas loss of ketene leads to m/z 191 (29%). A possible route to m/z 190 is explained in scheme 9:



Scheme 9

Of the molecules depicted in Scheme 6 only **23** and its reduction product **16** deserve a short comment: in **23** ($M^{+\cdot}$ = m/z 265) benzylic cleavage leads to the base peak at m/z 91, (benzyl/tropylium ion), whilst the corresponding cation comprises only 1% rel. int., probably on account of its electron withdrawing groups. In **16** these groups are absent. Therefore, we expected to find a high portion of the total ion current attributed to the dihydroisoindolylmethyl-cation (fragment **A**, m/z 146). Unfortunately, in the ms of compound **16**, too, m/z 146 carries only 13% rel. intensity at 70 eV, whereas m/z 145 is the base peak. In addition, **16** ($M^{+\cdot}$ = m/z 237) with a bisbenzylic bond shows some more abnormalities: it loses 105 mu (C_6H_5-CH_2-CH_2·) to m/z 132 and benzene to m/z 159 directly from $M^{+\cdot}$. The formation of the ion at m/z 132 is explained by a [1.3]H-shift (Scheme 10):



Scheme 10

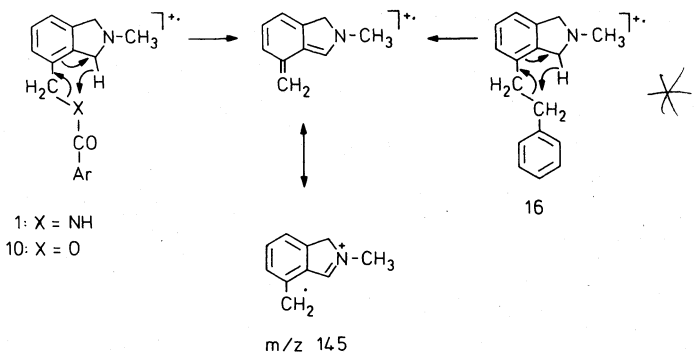
The ion at m/z 159 is the fragment with the highest rel. int. (82%) in the 12 eV spectrum. Its contribution to the total ion current is decreased with increasing electron energies.

The ion at m/z 159 may come up either by H-transfer from C-3 of $M^{+\cdot}$ onto the benzene ring (route A) or after a [1.3]H-shift in the side chain (route B) (Scheme 11):

A similar loss of benzene is found in the case of 4-benzyl-1,2,3,4-tetrahydroisoquinolines[16].

The problem: m/z 145 versus m/z 146

As already stated, the target molecules **1**, **10**, and **16** do not form the fragment ions at m/z 146 with sufficient intensity. The formation of the ion at m/z 145, interfering with the solution of our problem (see introductory remarks), is favoured. This is explained by a preceding and/or synchronous H-migration and subsequent elimination of benzylamide, p-nitrobenzoic acid, or toluene, respectively. The stability of the resulting immonium ion (m/z 145) may be the driving force of these processes (Scheme 12):

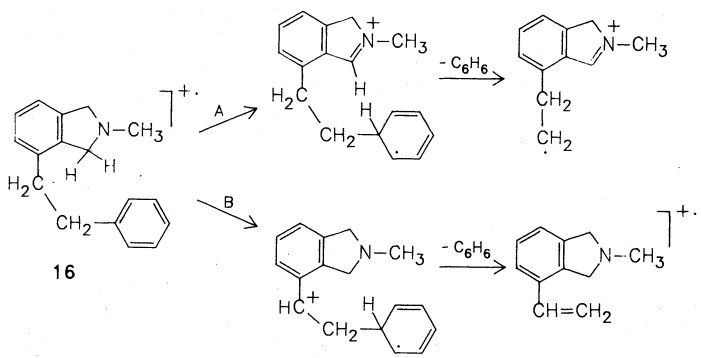


Scheme 12

The authors gratefully acknowledge the financial support received from Fonds der Chemischen Industrie, Frankfurt am Main.

Experimental Part

Melting points: apparatus according to Dr. Tottoli (Büchi), not corrected. - IR-spectra: Beckman Acculab III, KBr, if not stated otherwise. - UV-spectra: Uvikon 810 (Kontron), methanol, 1 cm. - ^{1}H-NMR-spectra: Varian EM 390 (90 MHz), 35 °; Bruker WM 250 (250 MHz), 24 °. If not stated otherwise data refer to 90 MHz spectra in ($CDCl_3$), TMS as int. standard. - Mass spectra: Varian MAT CH5. In general, signals with rel. int. <5% are not recorded. Rel. int. - usually not corrected - and metastable ions in brackets. Varian MAT 311/SS 200: B/E, B^2/E, CID-, FD- and high resolution (HR) MS. Varian MAT 112 S/SS 200: CI-MS. - Temp. in °C.



Scheme 11

2,3-Dihydro-2-methyl-4-nitro-1H-isoindole-1,3-dion (**3**)

The procedure of *Williams*[6] was slightly altered, for details see Ph.D. Thesis F. Knefeli, Regensburg 1987. - 73% yield, mp. 112° (lit.[6]: 111 - 112 °).

4-Amino-2,3-dihydro-2-methyl-1H-isoindole (**4**)

3.0 g (80 mmol) **3** in 40 ml of absol. THF were added dropwise to a suspension of 3.3 g $LiAlH_4$ in 40 ml of absol. THF. After stirring for 30 min at room temp. and refluxing for 90 min the mixture was decomposed with ice water. The precipitate was extracted with CH_2Cl_2, and the solvent evaporated in vacuo. The residue was dissolved in CH_2Cl_2, washed with saturated NaCl solution and dried over Na_2SO_4. The solvent was evaporated in vacuo. The residue became tarry very quickly. Therefore, it was used without purification for further experiments. For analytical purposes a sample was purified by Kugelrohr distillation at 120 - 130 ° (bath temp.), 0.01 Torr. - $C_9H_{12}N_2$ (148.2). - MS (HR): m/z 148 ($M^{+\cdot}$) $C_9H_{12}N_2$ calcd. 148.1001 found 148.0996; m/z 147 $C_9H_{11}N_2$ calcd. 147.0922 found 147.0920; m/z 146 $C_9H_{10}N_2$ calcd. 146.0844 found 146.0845; m/z 132 a) $C_8H_8N_2$ (75%) calcd. 132.0688 found 132.0688, b) $C_9H_{10}N$ (25%) calcd. 132.0813 found 132.0797; m/z 131 a) C_9H_9N (65%) calcd. 131.0735 found 131.0732, b) $C_8H_7N_2$ (35%) calcd. 131.0609 found 131.0613; m/z 130 C_9H_8N calcd. 130.0657 found 130.0661. - IR (film): 3340; 3210 (NH) cm^{-1}. - UV (qual.): λmax = 283; 237 nm. - ^{1}H-NMR: δ (ppm) = 2.59 (s, 3H, NCH_3), 3.54 (s, br., 2H, D_2O exchange, NH_2), 3.81 (AA', 2H, C-3), 3.92 (s, br., 2H, C-1), 6.45 - 6.58 (ABB' - "d", C-5), 6.58 - 6.72 (ABB' - "d", C-7), 6.92 - 7.15 (ABB'-"t", C-6). - MS (12 eV) m/z = 148 (100, $M^{+\cdot}$), 147 (9), 146 (11). - (70 eV): m/z = 148 (86, $M^{+\cdot}$), 147 (100, *146.01), 146 (55, *145.01), 145 (17, *144.01), 133 (7), 132 (48, *118.53), 131 (48, *116.74), 130 (19), 120 (12), 119 (9), 118 (11), 107 (17), 106 (16), 104 (17), 91 (8), 78 (7), 77 (18), 73.5 (15), 73 (24).

4-Cyano-2,3-dihydro-2-methyl-1H-isoindole (**5a**)

CuCl, prepared from 3.5 g $CuSO_4 \cdot 5H_2O$, 0.9 g NaCl, 0.75 g $NaHSO_3$, and 0.49 g NaOH according to *Marvel*[17], was dissolved in a solution of 1.81 g NaCN in 3 ml of water. After addition of benzene (25 ml), the mixture was cooled to 0 - 5 °. - To 1.65 g (11 mmol) crude amine **4** (75% of the theoretical amount), dissolved in 45 ml 2N H_2SO_4, were added 4.5 ml of 2.5 M $NaNO_2$ drop by drop below 5 °. This solution was added dropwise to the CuCl-solution at 0 °, then the mixture was stirred at 0 ° for 1 h, for 2 h at room temp., and finally for 1 h at 60 - 70 °. After cooling the mixture was made alkaline and extracted with ether. The org. layer was dried (Na_2SO_4) and the ether evaporated: 0.9 g crude **5a**, purification bei column chromatography (cc) (alumina, EtOAc; rf = 0.87, positive reaction with *Dragendorff*-reagent): 230 mg of a reddish oil. - $C_{10}H_{10}N_2$ (158.2). - IR (film): 2250 cm^{-1} (CN). - ^{1}H-NMR: δ (ppm) = 2.60 (s, 3H, NCH_3), 3.98 and 4.08 (2s, br., 2H each, $ArCH_2NCH_2Ar$), 7.16 - 7.60 (m, 3H, ArH). - MS (12 eV): m/z = 158 ($M^{+\cdot}$), 157. - (70 eV): m/z = 158 ($M^{+\cdot}$), 157 (*156.01), 142 (*128.43).

4-Aminomethyl-2,3-dihydro-2-methyl-1H-isoindole (**6**)

a) 225 mg (1.4 mmol) **5a** in 5 ml of absol. THF were reduced with 250 mg $LiAlH_4$ in 5 ml of absol. THF as described for **3**: 195 mg (85%) oily **6**; for analytical purposes a sample was distilled bulb-to-bulb (130 °/0.4 Torr) affording a colourless oil.

b) By analogous $LiAlH_4$ reduction of nitrile **8** (see below) besides some carbinol **9**.

$C_{10}H_{14}N_2$ (162.2). - IR (film): 3360; 3270 cm^{-1} (NH_2). - UV: λmax (log ε) = 274 (2.47), 266 nm (2.47). - ^{1}H-NMR: δ (ppm) = 1.80 (s, br. 2H, NH_2, D_2O exchange), 2.61 (s, 3H, NCH_3), 3.81 (s, 2H, $ArCH_2NCH_3$), 3.96 (s, br., 4H, $ArCH_2NCH_3$ and $ArCH_2NH_2$), 6.98 - 7.36 (m, 3H, ArH). - MS (12 eV): m/z = 146 (12), 145 (100). - (70 eV): m/z = 161 (3), 160 (3), 159 (3), 146 (12), 145 (100), 144 (64, *143.01), 132 (9), 131 (9), 130 (10).

4-Amino-2,3-dihydro-2-methyl-1H-isoindole-1,3-dione (**7**)

7 was prepared according to *Dabard*[7] in 89% yield, mp. 200 ° (lit.[7]: 199 °).

4-Cyano-2,3-dihydro-2-methyl-1H-isoindole-1,3-dione (**8**)

The CuCN solution was prepared from 4.62 g $CuSO_4 \cdot 5H_2O$ and 1.2 g NaCl in 16 ml H_2O, and from a solution of 0.98 g $NaHSO_3$ and 0.65 g NaOH in 8 ml H_2O as described above, followed by dissolution of the precipitate in 2.39 g NaCN dissolved in 4 ml H_2O. To finely powdered amine **7** (2g, 11 mmol), suspended in 40 ml of 2N H_2SO_4, cooled to 0 - 5 °, were slowly added 4.6 ml of 2.5 M $NaNO_2$. Parts of **7** were dissolved. For neutralization Na_2CO_3 was added carefully keeping the temp. below 5 ° (cf.lit.[18,19]).

After addition of 15 ml of benzene to the CuCN solution the solution of the diazonium salt was added as described. - After purification by cc (SiO_2,CH_2Cl_2) and crystallization from EtOH: 187 mg (9%) **8**, mp. 182 °. - $C_{10}H_6N_2O_2$ (186.2). - MS (HR): m/z 186 ($M^{+\cdot}$) $C_{10}H_6N_2O_2$ calcd. 186.0429 found .0426; m/z 157 $C_9H_5N_2O$ calcd. 157.0402 found .0395; m/z 142 $C_9H_6N_2$ calcd. 142.0531 found .0536; m/z 129 $C_8H_5N_2$ calcd. 129.0453 found .0455. - IR: 2265 (CN); 1780; 1715 (CO) cm^{-1}. - UV: λmax (log ε) = 281 (3.39), 219 nm (4.27). - ^{1}H-NMR: δ (ppm) = 3.24 (s, 3H, NCH_3), 7.78 - 8.23 (m, 3H, ArH). - MS (12 eV): m/z = 187 (42), 186 (100, $M^{+\cdot}$). - (70 eV): m/z = 187 (21), 186 (100, $M^{+\cdot}$), 185 (19), 158 (21), 157 (19, *156.01), 142 (66), 131 (14), 130 (14), 129 (62), 115 (7), 103 (38), 102 (22), 101 (70), 100 (14), 99 (12).

4-(N-Benzoyl-aminomethyl)-2,3-dihydro-2-methyl-1H-isoindole (**1**)

65 mg (0.4 mmol) **6** in 5 ml $CHCl_3$ were stirred with 128 mg benzoyl chloride and 100 mg finelly powdered Na_2CO_3 in 2 ml $CHCl_3$ for 0.5 h at room temp. then for 1 h at reflux temp. Usual work-up and cc (SiO_2, first CH_2Cl_2, then MeOH for elution of **1**) afforded 45 mg (42%) white crystals, mp. 170 °. - $C_{17}H_{18}N_2O$ (266.3). - calcd. C 76.7 H 6.81 N 10.5 found C 76.4 H 6.67 N 10.3. - IR: 3240; 3070 (NH); 2800 (CH); 1660 (amide I); 1560 (amide II) cm^{-1}. - UV: λmax (log ε) = 273 (3.03), 220 nm (4.20). - ^{1}H-NMR ($CDCl_3$+d_6-DMSO): δ (ppm) = 2.51 (s, 3H, NCH_3), 3.88 and 3.93 (2s, br. 2H each, CH_2NCH_2), 4.49 (d, J = 6 Hz, 2H, $ArCH_2NH$), 7.02 - 7.25 (m, 3H, ArH), 7.32 - 7.61 (m, 3H, ArH), 7.77 - 8.05 (m, 2H, ArH), 8.63 (t, J = 6 Hz, 1H, NH). - MS (70 eV): m/z = 265 (< 1%), 264 (< 1%), 146 (16), 145 (100), 144 (32), 133 (9), 132 (44), 131 (7), 130 (5), 122 (18), 121 (32) 105 (37), 77 (52).

1,2,3,6-Tetrahydro-3-methyl-phthalic anhydride (**11**)

11 was prepared according to *Frank*[10] in 71% yield, mp. 61 ° as described.

3-Methyl-phthalic anhydride (**12**)

12 was obtained from **11** by addition of bromine and HBr elimination as reported by *Newman*[11].

2,3-Dihydro-2,4-dimethyl-1H-isoindole-1,3-dione (**13**)

4.5 g **12** and 1.9 g methylamine-HCl were refluxed in 15 ml of glacial AcOH for 3 h. After evaporation i. vac. the residue was dried over KOH and recrystallized from EtOH: 4.13 g (85%) white needles, mp. 93 °. - $C_{10}H_9NO_2$ (175.2). - calcd. C 68.5 H 5.18 N 8.0 found C 68.0 H 5.13 N 8.0. - MS (HR): m/z 175 ($M^{+\cdot}$) $C_{10}H_9NO_2$ calcd. 175.0633 found .0638; m/z 118 (90% C_8H_6O) calcd. 118.0419 found .0420; (10% C_8H_8N) calcd. 118.0657 found .0658. - IR: 1770; 1710 cm^{-1} (CO). - UV: λmax (log ε) =

304 (3.44), 241 (3.97), 228 nm (4.02). - ^{1}H-NMR: δ (ppm) = 2.69 (s, 3H, $ArCH_3$), 3.14 (s, 3H, NCH_3), 7.35 - 7.77 (m, 3H, ArH). - MS (12 eV): m/z = 175 ($M^{+\cdot}$). - (70 eV): m/z = 175 (100, $M^{+\cdot}$), 174 (10), 157 (1, *140.85), 147 (10, *123.48), 146 (19), 132 (8), 131 (20), 119 (13), 118 (70, *95.37), 116 (9, *102.75), 91 (12), 90 (36, *68.64), 89 (33).

4-Bromomethyl-2,3-dihydro-2-methyl-1H-isoindole-1,3-dione (**14**)

2.0 g (11 mmol) **13** and 2.1 g N-bromosuccinimide (NBS) were dissolved in 20 ml of absol. CCl_4. The reaction was started by addition of 5 drops of tert.-butylhydroperoxide and warming. After reflux for 2 h additional 0.5 g NBS were added and refluxing was continued for 2 h. Progress of the reaction was controlled by tlc (SiO_2, CH_2Cl_2; rf = 0.6).

The hot solution was filtered with suction, the residue was washed and recrystallized from CCl_4: 1.55 g (54%) white needles, m. 142 °. - $C_{10}H_8BrNO_2$ (254.1). - calcd. C 47.3 H 3.17 N 5.5 found C 47.0 H 3.30 N 5.4. - IR: 1770; 1710 cm^{-1} (CO). - UV: λmax (log ε) = 302 (3.28), 222 nm (4.50). - ^{1}H-NMR: δ (ppm) = 3.18 (s, 3H, NCH_3), 4.96 (s, 2H, $ArCH_2Br$), 7.62 - 7.91 (m, 3H, ArH). - MS (10 eV): m/z = 253 (67, $M^{+\cdot}$, ^{79}Br), 174 (100). - (15 eV): m/z = 253 (33, $M^{+\cdot}$, ^{79}Br), 174 (100), 147 (4). - (70 eV): m/z = 253 (27, $M^{+\cdot}$, ^{79}Br), 174 (100), 147 (15, *124.19), 146 (6), 119 (16), 118 (13).

4-Acetoxymethyl-2,3-dihydro-2-methyl-1H-isoindole-1,3-dione (**15**)

320 mg (1.26 mmol) **14** and 250 mg freshly molten and powdered sodium acetate in 10 ml glacial acetic acid were refluxed for 24 h. The reaction was controlled by tlc (SiO_2, diisopropyl ether; rf = 0.5). The solution was diluted with ice water and extracted with Et_2O. The org. phase was washed with 2N NaOH and saturated NaCl solution, dried (Na_2SO_4) and evaporated. The homogenous residue was recrystallized from EtOH/EtOAc: 230 mg (90%) white needles, mp. 115 °. - $C_{12}H_{11}NO_4$ (233.2). - calcd. C 61.8 H 4.75 N 6.0 found C 61.6 H 4.88 N 5.9. - IR: 1770; 1750; 1715 cm^{-1} (CO). - UV: λmax (log ε) = 299 (3.30), 241 (4.01), 220 nm (4.55). - ^{1}H-NMR: δ (ppm) = 2.16 (s, 3H $COCH_3$), 3.18 (s, 3H, NCH_3), 5.61 (s, 2H, $ArCH_2O$), 7.59 - 7.92 (m, 3H, ArH). - MS (12 eV): m/z = 233 (2, $M^{+\cdot}$), 191 (43), 190 (100). - (70 eV): m/z = 233 (<1, $M^{+\cdot}$), 191 (29), 190 (100, *154.94), 188 (6, *186.02), 174 (5), 162 (11, *137.40), 161 (5).

2,3-Dihydro-4-hydroxymethyl-2-methyl-1H-isoindole (**9**)

374 mg (1.86 mmol) **15** in 10 ml of absol. THF were reduced by dropping to a solution of 425 mg $LiAlH_4$ in 10 ml of THF and worked up as usual: 230 mg (76%) solid material, homogenous in tlc (alumina, Et_2O; rf = 0.28), recrystallization from EtOAc: colourless needles, mp. 116 - 117 °. - $C_{10}H_{13}NO$ (163.2). - calcd. C 73.6 H 8.03 N 8.6 found C 73.3 H 8.12 N 8.5. - MS-HR: m/z 163 ($M^{+\cdot}$) $C_{10}H_{13}NO$ calcd. 163.0997 found .0993; m/z 162 $C_{10}H_{12}NO$ calcd. 162.0919 found .0915; m/z 145 $C_{10}H_{11}N$ calcd. 145.0892 found .0891; m/z 144 $C_{10}H_{10}N$ calcd. 144.0813 found .0813. - IR: 3130 (OH); 2810 (CH) cm^{-1}. - UV: λmax (log ε) = 274 (2.95), 266 (2.95), 202 nm (4.20). - ^{1}H-NMR: δ (ppm) = 2.52 (s; 3H, NCH_3), 3.55 and 3.86 (2s, 2H each, $ArCH_2NCH_2$), 4.25 (s, 2H, CH_2OH), 4.88 (s, br., D_2O exchange, 1H, OH), 6.98 - 7.34 (m, 3H, ArH). - MS (10 eV): m/z = 163 (79, $M^{+\cdot}$), 162 (64), 161 (8), 146 (14), 145 (100). - (70 eV): m/z = 163 (30, $M^{+\cdot}$), 162 (85, *161.01), 161 (5), 160 (6), 146 (9), 145 (60, *128.99), 144 (100, *143.01), 133 (5), 132 (43, *107.56), 131 (21), 130 (12), 117 (16, *103.70), 116 (5), 115 (6).

2,3-Dihydro-2-methyl-4-(4-nitrobenzoyloxymethyl)-1H-isoindole (**10**)

50 mg p-nitrobenzoyl chloride were added to 40 mg (0.245 mmol) **9** in 1 ml of absol. pyridine. After 2 h at room temp. the pyridine was distilled off and the residue was purified by cc (alumina, CH_2Cl_2; rf = 0.5, *Dragendorff* reaction positive): 69 mg (90%) orange-yellow oil. Crystallization from Et_2O: orange-yellow crystals, mp. 103 °. - $C_{17}H_{16}N_2O_4$ (312.3). calcd. C 65.4 H 5.16 N 9.0 found C 65.3 H 5.12 N 8.9. - IR: 2780 (CH); 1720 (CO); 1535; 1360 (NO_2) cm^{-1}. - UV: λmax (log ε) = 335 (2.63), 307 (2.86), 260 (3.66), 212 nm (3.75). - ^{1}H-NMR: δ (ppm) = 2.61 (s, 3H, NCH_3), 3.97 and 4.01 (2s, 2H each, CH_2NCH_2), 5.35 (s, 2H, $ArCH_2O$), 7.14 - 7.39 (m, 3H, ArH), 8.12 - 8.42 (m, 4H, NO_2-ArH). - MS (12 eV): m/z = 312 (4, $M^{+\cdot}$), 311 (14), 181 (5), 167 (6), 146 (13), 145 (100). - (70 eV): m/z = 312 (<1, $M^{+\cdot}$), 311 (5), 310 (4), 181 (4), 167 (4), 150 (11), 146 (16), 145 (100), 144 (54), 132 (8), 131 (7), 130 (6).

6-Phenyl-1,3-hexadiene (**17**)

13 g freshly molten and finely powdered $KHSO_4$ were placed in a 100 ml 3-necked flask, equipped with a dropping funnel, a short condenser and an ice-cooled receiver. 8.12 g (46 mmol) of 6-phenyl-1-hexene-3-ol[12] were filled into the dropping funnel, the apparatus was evaporated (<12 torr) and the 3-necked flask was heated to 150 ° by dipping it into an oil bath. Then 6-phenyl-1-hexene-3-ol was dropped to $KHSO_4$ very slowly (4 - 6 h). The distillate in the receiver (org. and aqueous phase) was diluted with water and Et_2O and separated. The org. layer was dried (Na_2SO_4) and evaporated. The residue was fractionated by distillation: 3 g (67%) colourless liquid, 95 °/12 torr; the material has a low viscosity and tends to polymerize. Therefore, it was processed without further chracterization. - $C_{12}H_{14}$ (158.2). - IR (film): 1640; 1600 cm^{-1} (C=C). - UV: λmax (log ε) = 272 (2.52), 268 (2.63), 261 (2.69), 228 nm (3.93).

1,2,3,6-Tetrahydro-3-(2-phenylethyl)-phthalic anhydride (**18**)

18 was prepared from crude **17** and maleic anhydride as reported[12].

3-(2-Phenylethenyl)-phthalic anhydride (**19**)

To 300 mg (1.2 mmol) **18** in 4 ml of glacial acetic acid 0.5 ml Br_2 in 2 ml of AcOH were added drop by drop under stirring at 90 ° - 110 °. After further stirring for 20 h at 110 ° AcOH was evaporated in vacuo and the residue was heated to 190 ° for 10 h. Thereafter **18** could not longer be detected by tlc (1. fluoresceine, 2. 5% Br_2 in CCl_4). - Crude **19** was dissolved in CH_2Cl_2, washed with saturated NaCl solution and dried (Na_2SO_4). The solvent was evaporated. After cc (SiO_2, CH_2Cl_2; fluorescence at 366 nm) crude **19** was crystallized from benzene/petrolether (40 °/60 °): faint yellow crystals, mp. 164 - 166 °. - $C_{16}H_{10}O_3$ (250.3). - calcd. C 76.8 H 4.03 found C 76.6 H 3.98. - IR: 1840; 1770 cm^{-1} (CO). - ^{1}H-NMR: δ (ppm) = 7.09 - 8.31 (m, 10H). - MS (12 eV): m/z = 250 ($M^{+\cdot}$). - (70 eV): m/z = 250 (100, $M^{+\cdot}$), 222 (10, *197.14), 206 (9), 205 (9), 194 (19), 178 (30), 177 (12), 176 (16), 164 (14).

2,3-Dihydro-2-methyl-4-(2-phenylethenyl)-1H-isoindole-1,3-dione (**21**)

180 mg (0.72 mmol) **19** and 100 mg methylamine-HCl in 5 ml of glacial acetic acid were refluxed for 5 h. Then the mixture was poured onto crushed ice and extracted three times with CH_2Cl_2. The org. layer was washed with 2N NaOH and with saturated NaCl solution, dried (Na_2SO_4) and evaporated: 156 mg (82%) oily material which was purified by cc (SiO_2/CH_2Cl_2). - $C_{17}H_{13}NO_2$ (263.3). - calcd. C 77.6 H 4.98 N 5.3 found C 77.3 H 5.04 N 5.2. - IR: 1770; 1710 cm^{-1} (CO). - UV (qual.): λmax = 356; 283; 227 nm. - ^{1}H-NMR: δ (ppm) = 3.17 (s, 3H, NCH_3), 7.15 - 8.47 (m, 10H, ArH, CH=CH). - MS (12 eV): m/z = 263 ($M^{+\cdot}$). - (70 eV): m/z = 263 (100, $M^{+\cdot}$), 262 (38, *261.00), 234 (10), 207 (8), 206 (17), 205 (32), 186 (10), 179 (8), 178 (36), 177 (18), 176 (17), 152 (7), 151 (8).

2,3-Dihydro-2-methyl-4-(2-phenylethenyl)-1H-isoindole (**22**)

80 mg (0.3 mmol) **21** in 5 ml of absol. THF were reduced with 70 mg $LiAlH_4$ dissolved in 5 ml of absol. THF at 0 ° as described. - Crude **22** was

purified by cc (alumina, CH_2Cl_2, *Dragendorff* reagent positive): 30 mg (42%) yellow oil. - $C_{17}H_{17}N$ (235.3). - ^{1}H-NMR: δ (ppm) = 2.60 (s, 3H, NCH_3), 3.93 and 4.08 (2s, br., 2H each, CH_2NCH_2), 6.99 - 7.60 (m, 10H, ArH, CH=CH). - MS (12 eV): m/z 235 (100, $M^{+\cdot}$), 234 (64), 233 (11). - (70 eV): m/z 235 (62, $M^{+\cdot}$), 234 (100), 233 (6), 232 (7), 219 (5), 218 (6), 217 (6), 203 (10), 202 (5), 193 (6), 191 (5), 190 (5), 189 (8), 178 (7).

2,3-Dihydro-2-methyl-4-(2-phenylethyl)-1H-isoindole-1,3-dione (**23**)

60 mg (0.23 mmol) **21** in 2 ml of MeOH and a few drops of CH_2Cl_2 were hydrogenated at room temp. and normal pressure over Pd/C 10% in 10 ml of MeOH. After 1 h the consumption of H_2 hat ceased; the mixture was filtered, the filtrate was evaporated in vacuo and the residue was dissolved in CH_2Cl_2, washed with saturated NaCl solution, and the solvent was distilled off almost to dryness. The residue crystallized and was homogeneous in tlc (SiO_2, CH_2Cl_2; rf = 0.4). Recrystallization from EtOH: 64 mg (76%) needles and plates, mp. 119 °. - $C_{17}H_{15}NO_2$ (265.3). - calcd. C 77.0 H 5.70 N 5.3 found C 76.9 H 5.85 N 5.2. - IR: 1775; 1710 cm^{-1} (CO). - UV: λmax (log ε) = 305 (3.43), 241 (4.02), 222 nm (4.39). - ^{1}H-NMR: δ (ppm) = 2.80 - 3.06 (m, 2H, $ArCH_2CH_2Ph$), 3.15 (s, 3H, NCH_3), 3.26 - 3.50 (m, 2H, $ArCH_2CH_2Ph$), 7.06 - 7.78 (m, 8H, ArH). - MS (12 eV): m/z = 265 (100, $M^{+\cdot}$), 187 (1), 91 (4). - (70 eV): m/z = 265 (60, $M^{+\cdot}$), 250 (1), 187 (2), 174 (1), 91 (100), 65 (6, *46.42).

2,3-Dihydro-2-methyl-4-(2-phenylethyl)-1H-isoindole (**16**)

a) **22** was hydrogenated over Pd/C as described for **21**.

b) 50 mg (0.19 mmol) **23** in 4 ml of absol. THF were reduced with 45 mg $LiAlH_4$ in 5 ml of absol. THF at 0 ° as described: 42 mg of crude, unstable (!) **16**, which was purified by cc (alumina, EtOAc), prep. tlc (SiO_2, CH_2Cl_2/MeOH 95 + 5), and Kugelrohr-distillation: 15 mg (34%) colourless oil. - $C_{17}H_{19}N$ (237.3). - calcd. C 86.0 H 8.07 N 5.9 found C 85.5 H 8.17 N 5.7. - ^{1}H-NMR (250 MHz): δ (ppm) = 2.59 (s, 3H, NCH_3), 2.82 - 2.90 (AA'BB', 4H, $ArCH_2CH_2Ar$), 3.85 and 3.95 (2s, br., 2H each, CH_2NCH_2), 6.99 - 7.31 (m, 8H, ArH). - MS (12 eV): m/z = 237 (100, $M^{+\cdot}$), 236 (25), 235 (21), 160 (11), 159 (81), 145 (5), 144 (2), 133 (7), 132 (75). - (15 eV): m/z = 237 (100, $M^{+\cdot}$), 236 (81), 235 (14), 160 (13), 159 (62), 158 (5), 146 (7), 145 (18), 144 (7), 133 (14), 132 (78). - (70 eV): m/z = 237 (34, $M^{+\cdot}$), 236 (89, *235.00), 235 (7), 231 (7), 230 (5), 160 (6), 159 (50), 158 (14), 146 (13), 145 (100), 144 (97, *143.01), 143 (5), 133 (10), 132 (94), 131 (12), 130 (9), 117 (8), 116 (6), 115 (14), 105 (13), 103 (16), 91 (20).

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[Ph578]