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 cleavage¹.

This unexpected behaviour points towards functional group interaction in the M^+ prior to bond breaking, an assumption supported by the fact that the percentage of the total ion current corresponding to the $(M-X)^+$ -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 dihydroisoindo-lylmethyl 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 \mathbf{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 Spectroscopy³).

^{*} Part IV: see lit.¹⁾.

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Scheme 2

1 was prepared on two routes:

Method I

(Substituted) phthalic anhydrides react with methylamine to the corresponding N-methylphthalimides⁴). Subsequent reduction with LiAlH₄ leads to 2,3-dihydro-2-methyl-1H-isoindoles⁵) (Scheme 3):





The nitrophthalimide 3, prepared from 2 according to $Williams^{6)}$ in 73% yield, was reduced to 4 with 1 mole of LiAlH₄. 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[•]) from M⁺.

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 7⁷). 7 is a very weak base (phenylogous amide): even washing of the crude white hydrochloride with water liberated the yellow base ($\lambda max = 387$ 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 (λ max = 281 nm) as expected. Its M⁺ loses CO₂ (see "Mass Spectra"). 8 was reduced with LiAlH₄ 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. intensities⁹⁾. Therefore, we expected the p-nitrobenzoate 10 to be a suitable precursor of ion A.

2) 3-Dihydro-2-methyl-4-(4-nitrobenzoyloxymethyl)-1Hisoindole (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 Br₂ with subsequent elimination of HBr according to New-man¹¹ (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 LiAlH₄ 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 ¹³C-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 described¹²⁾. So we varied the route of Scheme 5, as depicted in Scheme 6:

The diene 17 is prepared by dehydration of 6-phenyl-1hexene-3-ol¹²⁾ with KHSO₄ 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^+ 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-2methyl-1H-isoindole (4) is characterized by the base peak at m/z 147 (M-H⁻)⁺ 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[·] - CH_3)^{+·}, established by *118.53, the remaining 25% are represented by $C_9H_{10}N$ (M - NH_2)⁺. Analogously, the peak at m/z 131 (48% rel. int.) consists of 35% $C_8H_7N_2$ (M - 2H - 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 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)⁺-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^+ prior to fragmentation (Scheme 8):





The ion at m/z 142 (66%; HR: $C_9H_6N_2$) is in accordance with $(M - CO_2)^+$. This assumption is corroborated by metastable ion analysis: B/E-linked scans of M^+ . (m/z 186) indicate its correlation with m/z 142, B²/E-linked scans show that m/z 142 originates directly from M^+ . The wide dish-shaped peak³⁾ of M^+ in the B²/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 CO₂ from N-methyl- and N-phenyl-phthalimides is known¹⁴, thermal rearrangements prior to ionization have been excluded^{14,15}.

At 10 eV M⁺ 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 ¹³C-satellite of m/z 145), at 70 eV it carries only <2% rel. intensity. The (M - H)⁺-ion ejects 30 mu (CH₂O) 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 ¹³C-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** ($M^{+} = m/z$ 175, 100%) loss of CO₂ is prominent and explained analogously to that of **8**. The most intense fragment ion is at m/z 118; HR indicates C₈H₈N and C₈H₆O. It originates from m/z 146 which loses CO (*95.37) and from m/z 147 by loss of CH₃N. The precursor ion at m/z 146 arises from M⁺ by a) loss of CH₃N (29 u) and b) by loss of CO (28 u), producing the ion at m/z 147 (10%; *123.48), which loses H to m/z 146. Interaction of the carbonyl-oxygen with the CH₃-group in the peri-position causes H₂O-elimination from M⁺ affording the ion at m/z 157 (1%; *140.85).

In the ms of the bromomethyl-phthalimide 14, the fragment ion $(M - Br)^+$ 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^+ 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 CH₃-CO⁻ instead of CH₃-COO⁻ (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 ($M^{+} = m/z$ 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 ($M^{+} = m/z$ 237) with a bisbenzylic bond shows some more abnormalities: it loses 105 mu (C_6H_5 -CH₂-CH₂) to m/z 132 and benzene to m/z 159 directly from M^{+} . 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^+ 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-tetrahydroisoquinolines¹⁶.

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

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Experimental Part

Melting points: apparatus according to Dr. Tottoli (Büchi), not corrected. - IR-spectra: Beckman Acculab III, KBr, if not stated otherwise. - UVspectra: Uvikon 810 (Kontron), methanol, 1 cm. - ¹H-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 (CDCl₃), 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, B²/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 LiAlH₄ 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 CH2Cl2, and the solvent evaporated in vacuo. The residue was dissolved in CH2Cl2, washed with saturated NaCl solution and dried over Na₂SO₄. 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⁺) $C_9H_{12}N_2$ calcd. 148.1001 found 148.0996; m/z 147 C9H11N2 calcd. 147.0922 found 147.0920; m/z 146 C₉H₁₀N₂ 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) C₉H₉N (65%) calcd. 131.0735 found 131.0732, b) $C_8H_7N_2$ (35%) calcd. 131.0609 found 131.0613; m/z 130 C9H8N calcd. 130.0657 found 130.0661. - IR (film): 3340; 3210 (NH) cm⁻¹. - UV (qual.): $\lambda max = 283$; 237 nm. - ¹H-NMR: δ (ppm) = 2.59 (s, 3H, NCH₃), 3.54 (s, br., 2H, D₂O exchange, NH₂), 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 (<u>ABB</u>'-"t", C-6). - MS (12 eV) m/z = 148 (100, M⁺), 147 (9), 146 (11). - (70 eV): m/z = 148 (86, M^{+.}), 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 CuSO₄ · 5H₂O, 0.9 g NaCl, 0.75 g NaHSO₃, and 0.49 g NaOH according to Marvel¹⁷⁾, 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 H₂SO₄, were added 4.5 ml of 2.5 M NaNO2 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 (Na₂SO₄) 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). - ¹H-NMR: δ (ppm) = 2.60 (s, 3H, NCH₃), 3.98 and 4.08 (2s, br., 2H each, ArCH2NCH2Ar), 7.16 - 7.60 (m, 3H, ArH). -MS (12 eV): m/z = 158 (M⁺), 157. - (70 eV): m/z = 158 (M⁺), 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 LiAlH₄ 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.

C₁₀H₁₄N₂ (162.2). - IR (film): 3360; 3270 cm⁻¹ (NH₂). - UV: λmax (log ε) = 274 (2.47), 266 nm (2.47). - ¹H-NMR: δ (ppm) = 1.80 (s, br. 2H, NH₂, D₂O exchange), 2.61 (s, 3H, NCH₃), 3.81 (s, 2H, ArCH₂NCH₃), 3.96 (s, br., 4H, ArCH₂NCH₃ and ArCH₂NH₂), 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 $Dabard^{2}$ 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 CuSO₄ \cdot 5 H₂O and 1.2 g NaCl in 16 ml H₂O, and from a solution of 0.98 g NaHSO₃ and 0.65 g NaOH in 8 ml H₂O as described above, followed by dissolution of the precipitate in 2.39 g NaCN dissolved in 4 ml H₂O. To finely powdered amine 7 (2g, 11 mmol), suspended in 40 ml of 2N H₂SO₄, cooled to 0 - 5°, were slowly added 4.6 ml of 2.5 M NaNO₂. Parts of 7 were dissolved. For neutralization Na₂CO₃ 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⁺) $C_{10}H_6N_2O_2$ 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: λ max (log ε) = 281 (3.39), 219 nm (4.27). - ¹H-NMR: δ (ppm) = 3.24 (s, 3H, NCH₃), 7.78 - 8.23 (m, 3H, ArH). - MS (12 eV): m/z = 187 (42), 186 (100, M⁺). - (70 eV): m/z = 187 (21), 186 (100, M⁺), 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 CHCl₃ were stirred with 128 mg benzoyl chloride and 100 mg finelly powdered Na₂CO₃ in 2 ml CHCl₃ for 0.5 h at room temp. then for 1 h at reflux temp. Usual work-up and cc (SiO₂, first CH₂Cl₂, then MeOH for elution of 1) afforded 45 mg (42%) white crystals, mp. 170 °. - C₁₇H₁₈N₂O (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). - ¹H-NMR (CDCl₃+d₆-DMSO): δ (ppm) = 2.51 (s, 3H, NCH₃), 3.88 and 3.93 (2s, br. 2H each, CH₂NCH₂), 4.49 (d, J = 6 Hz, 2H, ArCH₂NH), 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 $Newman^{(1)}$.

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°. C₁₀H₉NO₂ (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⁺) C₁₀H₉NO₂ calcd. 175.0633 found .0638; m/z 118 (90% C₈H₆O) calcd. 118.0419 found .0420; (10% C₈H₈N) calcd. 118.0657 found .0658. - IR: 1770; 1710 cm⁻¹ (CO). - UV: λ max (log ϵ) =

304 (3.44), 241 (3.97), 228 nm (4.02). - ¹H-NMR: δ (ppm) = 2.69 (s, 3H, ArCH₃), 3.14 (s, 3H, NCH₃), 7.35 - 7.77 (m, 3H, ArH). - MS (12 eV): m/z = 175 (M⁺). - (70 eV): m/z = 175 (100, M⁺), 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. CCl₄. 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 (SiO₂, CH₂Cl₂; rf = 0.6).

The hot solution was filtered with suction, the residue was washed and recrystallized from CCl₄: 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: λ max (log ε) = 302 (3.28), 222 nm (4.50). - ¹H-NMR: δ (ppm) = 3.18 (s, 3H, NCH₃), 4.96 (s, 2H, ArCH₂Br), 7.62 - 7.91 (m, 3H, ArH). - MS (10 eV): m/z = 253 (67, M⁺, ⁷⁹Br), 174 (100). - (15 eV): m/z = 253 (33, M⁺, ⁷⁹Br), 174 (100), 147 (4). - (70 eV): m/z = 253 (27, M⁺, ⁷⁹Br), 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 (SiO₂, diisopropyl ether; rf = 0.5). The solution was diluted with ice water and extracted with Et₂O. The org. phase was washed with 2N NaOH and saturated NaCl solution, dried (Na₂SO₄) and evaporated. The homogenous residue was recrystallized from EtOH/EtOAc: 230 mg (90%) white needles, mp. 115°. - C₁₂H₁₁NO₄ (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: λ max (log ε) = 299 (3.30), 241 (4.01), 220 nm (4.55). - ¹H-NMR: δ (ppm) = 2.16 (s, 3H COCH₃), 3.18 (s, 3H, NCH₃), 5.61 (s, 2H, ArCH₂O), 7.59 - 7.92 (m, 3H, ArH). - MS (12 eV): m/z = 233 (2, M⁺), 191 (43), 190 (100). - (70 eV): m/z = 233 (<1, M⁺), 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 LiAlH₄ in 10 ml of THF and worked up as usual: 230 mg (76%) solid material, homogenous in tlc (alumina, Et₂O; rf = 0.28), recrystallization from EtOAc: colourless needles, mp. 116 - 117 °. -C10H13NO (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⁺) C₁₀H₁₃NO calcd. 163.0997 found .0993; m/z 162 C10H12NO calcd. 162.0919 found .0915; m/z 145 C10H11N 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: λ max (log ε) = 274 (2.95), 266 (2.95), 202 nm (4.20). - ¹H-NMR: δ (ppm) = 2.52 (s; 3H, NCH₃), 3.55 and 3.86 (2s, 2H each, ArCH₂NCH₂), 4.25 (s, 2H, CH₂OH), 4.88 (s, br., D₂O exchange, 1H, OH), 6.98 - 7.34 (m, 3H, ArH). - MS (10 eV): m/z = 163 $(79, M^{+})$, 162 (64), 161 (8), 146 (14), 145 (100). - (70 eV): m/z = 163 (30, M^{+.}), 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, CH₂Cl₂; rf = 0.5, *Dragendorff* reaction positive): 69 mg (90%) orange-yellow oil. Crystallization from Et₂O: 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 (NO₂) cm⁻¹. - UV: λ max (log ε) = 335 (2.63), 307 (2.86), 260 (3.66), 212 nm (3.75). - ¹H-NMR: δ (ppm) = 2.61 (s, 3H, NCH₃), 3.97 and 4.01 (2s, 2H each, CH₂NCH₂), 5.35 (s, 2H, ArCH₂O), 7.14 - 7.39 (m, 3H, ArH), 8.12 - 8.42 (m, 4H, NO₂-ArH). - MS (12 eV): m/z = 312 (4, M⁺), 311 (14), 181 (5), 167 (6), 146 (13), 145 (100). - (70 eV): m/z = 312 (<1, M⁺), 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 KHSO₄ 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-ol¹²⁾ 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 KHSO₄ very slowly (4 - 6 h). The distillate in the receiver (org. and aqueous phase) was diluted with water and Et₂O and separated. The org. layer was dried (Na₂SO₄) 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. C₁₂H₁₄ (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 reported¹²⁾.

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

To 300 mg (1.2 mmol) **18** in 4 ml of glacial acetic acid 0.5 ml Br₂ 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% Br₂ in CCl₄). - Crude **19** was dissolved in CH₂Cl₂, washed with saturated NaCl solution and dried (Na₂SO₄). The solvent was evaporated. After cc (SiO₂, CH₂Cl₂; fluorescence at 366 nm) crude **19** was crystallized from benzene/petrolether (40 °/60 °): faint yellow crystals, mp. 164 - 166 °. - C₁₆H₁₀O₃ (250.3). - calcd. C 76.8 H 4.03 found C 76.6 H 3.98. - IR: 1840; 1770 cm⁻¹ (CO). - ¹H-NMR: δ (ppm) = 7.09 - 8.31 (m, 10H). - MS (12 eV): m/z = 250 (M⁺). - (70 eV): m/z = 250 (100, M⁺), 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 CH₂Cl₂. The org. layer was washed with 2N NaOH and with saturated NaCl solution, dried (Na₂SO₄) and evaporated: 156 mg (82%) oily material which was purified by cc (SiO₂/CH₂Cl₂). - C₁₇H₁₃NO₂ (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.): λ max = 356; 283; 227 nm. - ¹H-NMR: δ (ppm) = 3.17 (s, 3H, NCH₃), 7.15 - 8.47 (m, 10H, ArH, CH=CH). - MS (12 eV): m/z = 263 (M⁺). - (70 eV): m/z = 263 (100, M⁺), 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)

 $80 \text{ mg} (0.3 \text{ mmol}) 21 \text{ in 5 ml of absol. THF were reduced with 70 mg LiAlH₄ dissolved in 5 ml of absol. THF at 0 ° as described. - Crude 22 was$

purified by cc (alumina, CH₂Cl₂, *Dragendorff* reagent positive): 30 mg (42%) yellow oil. - $C_{17}H_{17}N$ (235.3). - ¹H-NMR: δ (ppm) = 2.60 (s, 3H, NCH₃), 3.93 and 4.08 (2s, br., 2H each, CH₂NCH₂), 6.99 - 7.60 (m, 10H, ArH, CH=CH). - MS (12 eV): m/z 235 (100, M⁺), 234 (64), 233 (11). - (70 eV): m/z 235 (62, M⁺), 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 CH₂Cl₂ were hydrogenated at room temp. and normal pressure over Pd/C 10% in 10 ml of MeOH. After 1 h the consumption of H₂ hat ceased; the mixture was filtered, the filtrate was evaporated in vacuo and the residue was dissolved in CH₂Cl₂, washed with saturated NaCl solution, and the solvent was distilled off almost to dryness. The residue crystallized and was homogeneous in tlc (SiO₂, CH₂Cl₂; rf = 0.4). Recrystallization from EtOH: 64 mg (76%) needles and plates, mp. 119°. - C₁₇H₁₅NO₂ (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). - ¹H-NMR: δ (ppm) = 2.80 - 3.06 (m, 2H, ArCH₂CH₂Ph), 3.15 (s, 3H, NCH₃), 3.26 - 3.50 (m, 2H, ArCH₂CH₂Ph), 7.06 - 7.78 (m, 8H, ArH). - MS (12 eV): m/z = 265 (100, M⁺), 187 (1), 91 (4). - (70 eV): m/z = 265 (60, M⁺), 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 LiAlH₄ 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 (SiO₂, CH₂Cl₂/MeOH 95 + 5), and Kugelrohr-distillation: 15 mg (34%) colourless oil. - C₁₇H₁₉N (237.3). - calcd. C 86.0 H 8.07 N 5.9 found C 85.5 H 8.17 N 5.7. - ¹H-NMR (250 MHz): δ (ppm) = 2.59 (s, 3H, NCH₃), 2.82 - 2.90 (AA'BB', 4H, ArCH₂CH₂Ar), 3.85 and 3.95 (2s, br., 2H each, CH₂NCH₂), 6.99 - 7.31 (m, 8H, ArH). - MS (12 eV): m/z = 237 (100, M⁺), 236 (25), 235 (21), 160 (11), 159 (81), 145 (5), 144 (2), 133 (7), 132 (75). - (15 eV): m/z = 237 (100, M⁺), 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⁺), 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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