# Electron Impact Induced Loss of C-5/C-8 Substituents of 1,2,3,4-Tetrahydroisoquinolines, VI1):

# Synthesis and Mass Spectrometric Fragmentation of Dihydroindole Derivatives<sup>\*)\*\*)</sup>

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The syntheses of the C-4 substituted dihydroindoles 25, 31 (scheme 7), and 36 (scheme 8) are described. - The CID MIKE spectrum in the 2. field free region (2. FFR) of m/z 146 from 25 is very similar to but not identical with that of m/z 146 from the C-5 substituted tetrahydroisoquinolines 3, 6, 7, and 8 (scheme 2), so supporting our hypothesis of a rearrangement in  $M^+$  of tetrahydroisoquinolines<sup>1)</sup> prior to fragmentation, but not proving it. As the CID MIKE spectra of the tetrahydroisoquinolines 3, 6, 7, and 8 are not identical among each other we assume that a 1.3-H-shift takes places in their  $M^+$  in competition to the rearrangement mentioned above.

Elektronenstoß-induzierter Verlust der Substituenten an C-5 und C-8 bei 1,2,3,4-Tetrahydroisochinolinen, 6. Mitt.<sup>1)</sup>:

Synthese und massenspektrometrische Fragmentierung von Dihydroindol-Derivaten

Die Herstellung der C-4-substituierten Dihydroindole **25**, **31** (Schema 7) und **36** (Schema 8) wird beschrieben. - Das CID MIKE-Spektrum im 2. feldfreien Raum (2. FFR) von m/z 146 aus **25** ist sehr ähnlich aber nicht identisch mit den entspr. Spektren von m/z 146 aus den C-5-substituierten Tetrahydroisochinolinen **3**, **6**, 7 und **8** (Schema 2). Dies stützt unsere Arbeitshypothese einer Umlagerung in den M<sup>+</sup> von Tetrahydroisochinolinen<sup>1)</sup> vor der Fragmentierung, beweist sie aber nicht. Da die CID MIKE-Spektren der Tetrahydroisochinoline **3**, **6**, 7 und **8** unter sich nicht identisch sind, nehmen wir an, daß ein 1.3-H-shift in den M<sup>+</sup> der Tetrahydroisochinoline zusätzlich zu der o. a. Umlagerung stattfindet.

At C-5 and / or C-8 substituted 1,2,3,4-tetrahydro-2-methylisoquinolines A lose these substituents upon EI ionisation probably giving rise to 2,3-dihydro-N-methyl-1H-isoindole-ions **B** or to 2,3-dihydro-N-methylindoleions **C**, respectively<sup>1)</sup> (scheme 1).



## Scheme 1

Recently we described some syntheses of C-4 substituted 2,3-dihydro-Nmethyl-1H-isoindoles which we supposed to be suitable precursors of ion **B**, and we reported on their electron impact induced fragmentation leading

\*) From the Ph.D. thesis Frank Knefeli, Regensburg 1987

\*\*) Dedicated with warm regards to Prof. Dr. H. Schönenberger, Regensburg, on the occasion of his 65th birthday.

unexpectedly to a H-transfer from C-3 to the side chain so forming a stable iminium ion with high relative intensity (rel. int.) instead of the carbenium ion  $B^{1}$ . Here we report on the synthesis of dihydro-indole precursors of ion C ( $R^8$ =H) and its comparison with the pertinent ions obtained from suitable C-5 substituted tetrahydroisoquinolines.

## Synthesis of C-5 substituted 1,2,3,4-tetrahydro-Nmethylisoquinolines

The key intermediate for these tetrahydroisoquinolines is 5-amino-1,2,3,4-tetrahydro-N-methylisoquinoline (1) which was obtained from isoquinoline via 5-nitroisoquinoline, its N-metho-iodide, reduction to 1,2,3,4-tetrahydro-2-methyl-5-nitroisoquinoline and its hydrogenation with Raney-Ni to 1 (scheme 2).

The most important fragmentation pathway in the ms of 1 is loss of 43 amu (retro-*Diels-Alder* (RDA) reaction) leading to the base peak at 70 eV. At lower ionization energies this fragment is formed with 29% (15 eV) and 16% (12 eV) rel. int., respectively, as it is expected for a high energy

process. Loss of  $NH_2$  (16%) is of minor importance. So, 1 is not a useful molecule for our experiments.

Therefore, we synthesized the C-5 substituted tetrahydroisoquinolines 2 - 8 starting from 1 (scheme 2):

Scheme 2

Compounds 2, 3, and 4 were obtained by *Sandmeyer* reaction. The ms of 2 and 4 revealed a contamination by the chloro compound 3 which is caused by CuCl formed concomitantly with CuBr and CuCN, respectively. This byproduct was removed from 2 by repeated recrystallization of 2-HCl. - In our hands *Clarke's* method<sup>2,3)</sup> worked best for the synthesis of 4.

The ms of 3 will be discussed in the ms section of this publication. - Curiously enough 4 lost CN' to m/z 146 (ion C, R<sup>8</sup>=H) with 1% rel. int. only. RDA-fragmentation gives rise to m/z 129 (30%). So, the ms of nitril 4 was not further studied.

Diazotation of 1 and heating of the corresponding diazonium salt afforded the phenol 5. - Its  $M^+$  decomposes at 70 eV on three main routes (scheme 3):





As indicated, the ion at m/z 146 is formed with 12% rel. int., at 12 eV it came up with 2% rel. int. only. Loss of H with consecutive loss of 2H (aromatization) is the prominent fate of  $M^+$  (70 / 12 eV). The ion  $(M-1)^+$  is strong (often base peak) in compounds 1 - 8 at low as well as at high electron energies.

Acetylation of 5 led to 6 which forms ion C ( $R^8=H$ ) with 20% rel. int. at 70 eV directly from M<sup>+</sup> as indicated by a metastable ion at m/z \*103.98. -

The methoxy derivative 7 was obtained in good yields by reacting phenol 5 with  $CH_2N_2$ . Selective methylation according to *Rodionov* gave 7 in low yield as did the decomposition of the diazonium salt of 1 by heating it in methanol. The yield of 7 from the reaction of 5 with methyl p-toluene-sulphonate was poor.

Analogously we got the ethyl ether 8 from 5 and diazoethane. The ethers 7 and 8 were used for CID-measurements (cf. ms section).

# Syntheses of C-4 substituted 2,3-dihydroindoles

## a) Somei's Approach

We intended to use 4-formylindole (9) as starting material. - A synthesis of this molecule is described by *Somei* et al.<sup>4,5)</sup>. They treated 2-methyl-5-nitroisoquinolinium iodide (10) with TiCl<sub>3</sub> under strict conditions and obtained 4-(methylaminomethyl)indole (11), probably by reduction of the nitro group and the immonium moiety followed by hydrolysis, rearrangement and dehydration. - Subsequently 11 was oxidized to 9 (scheme 4).





All our efforts to repeat this synthesis of 11 on a preparative scale failed: we got 2-methyl-5-nitro-1(2H)isoquinolone (12) and the corresponding 5-amino derivative 13 besides a minute quantity of 11 (78 mg from 960 mg of 10). Acetylation of the crude reaction mixture prior to work-up<sup>4</sup>) led to some N-acetate 14 (for details see lit.<sup>6</sup>). - The structure of 12 was confirmed by comparison with authentic material, obtained from 10 via its pseudocarbinol and subsequent oxidation with  $K_3[Fe(CN)_6]^{7,8)}$ . - The structure of 11 was verified by its ms, which reveals loss of H<sub>2</sub>C=NH probably via a six membered transition state (scheme 5).



Scheme 5

## b) Synthesis according to Batcho-Leimgruber 9,10)

This two-step-synthesis is a modification of *Reissert's* method<sup>11</sup>: An adequate o-nitrotoluene derivative is condensed with N,N-dimethylformamide dimethylacetal to the corresponding o-nitro-dimethylaminostyrene which is cyclized to the indole derivative during Pd catalyzed hydrogenation.

2,3-Dimethyl-nitrobenzene (15) was oxidized regiospecifically by  $CrO_3$  in  $Ac_2O$  to yield the diacetate 16 which was not used directly in the *Batcho-Leimgruber* condensation, because we were afraid of possible interference of the activated methyl groups of the acetate moieties<sup>10</sup>. Therefore, it was converted to the acetal 17<sup>12</sup>. However, we did not



## Scheme 6

reach the reported yield of  $18^{12}$  (33%). So, we modified this method by hydrolyzing 17 to the aldehyd 19 which was converted into the cyclic acetal 20 which proved to be superior to 17 in the *Maehr* modification<sup>12)</sup> of the *Batcho-Leimgruber* procedure: the indole 18 was obtained in 54% yield. In some cases the dioxolane group survived work-up producing 21, which can easily be cleaved to 18 by 0.5 N HCl (scheme 6).

We expected the benzylic bond: indole-CH<sub>2</sub>-CH<sub>2</sub>-C<sub>6</sub>H<sub>5</sub> to be prone to fragmentation upon EI-ionization yielding ion C ( $\mathbb{R}^8$ =H) with sufficient intensity. This side chain was introduced by *Wittig* reaction leading to the "stilbene" 22 as an E/Z-mixture which was hydrogenated to compound 23 (scheme 7):

There are various methods described for the hydrogenation of indoles to 2,3-dihydroindoles. Catalytic hydrogenation occasionally attacks the carbocycle or opens the ring<sup>13)</sup>, reduction with Sn/HCl or Zn/HCl leads to the desired 2,3-dihydroindoles, but generally the yields are low on account of the indoles' tendency for polymerization.

Therefore, we reduced the indole 23 by Marshall's method as described for reduction of enamines<sup>14</sup>) using NaBH<sub>4</sub> in acetic acid. MS and <sup>1</sup>H-NMR-spectra of the product revealed that the N-ethylated 2,3-dihydroindole 24 had been built. Transfer of this observation in order to get the Nmethylated target molecule failed: the reaction of 23 with NaBH<sub>4</sub> in formic acid led to a complex mixture from which only traces of 25 could be isolated. This result is in accordance with Gribble's report<sup>15)</sup> who got only 16% of 2,3-dihydro-N-methylindole from indole under similar conditions. -Our results led us to a two-step procedure: 23 was treated with pyridine-borane<sup>16)</sup>, but we avoided acidic conditions on account of the sensitivity of 23 (cf. Experim. Part) and obtained 26 nearly quantitatively. Among various types of N-methylation<sup>6)</sup> Grob's procedure (HCHO/H<sub>2</sub>/Raney-Ni<sup>17)</sup>) proved to be best: 25 was obtained from 26 in 93% yield.



Scheme 7

25 is very labile: it decomposes even by contact with air, obviously by dehydrogenation (van Urk reaction positive). 25  $\cdot$  HCl, however, is stable.

The structure of 25 was confirmed by <sup>1</sup>H-NMR spectroscopy: Besides the aromatic H's of the  $\beta$ -phenylethyl group there is a "t" at  $\delta = 7.05$  ppm of H-6. H-5 and/or H-7 resonate at 6.37 and 6.56 ppm as doublets (J = 7.7 Hz). Increment calculations attribute H-5 to the signal at 6.56 ppm and H-7 to that at 6.37 ppm. This is corroborated bei NOE results: irradiation into the N-CH<sub>3</sub>-singulett at  $\delta = 2.74$  ppm increases the intensity of the H-2 signal at 3.22 - 3.28 ppm as well as that of the doublet at 6.37 ppm. Because the distance of H-7/N-CH<sub>3</sub> is small enough (<3.5  $\cdot 10^{-10}$  m), the doublet at  $\delta$ = 6.37 ppm belongs to H-7.

The ms of 25 is in accordance with our expectations: benzylic cleavage generates the fragment at m/z = 146 with 62% rel. int. at 70 eV. For a detailed discussion see ms section.

Two more dihydroindoles expected to be suitable precursors of ion C ( $\mathbb{R}^8$ =H), were obtained from 1-benzyl-4-( $\beta$ -hydroxyethyl)indole p-toluenesulfonate 27<sup>\*</sup>) (scheme 7).

Reduction of 27 with LiAlH<sub>4</sub> led to the 4-ethylindole 28; the N-benzyl moiety in 28 could not be cleaved hydrogenolytically over Pd/C. This is described also for other Nbenzyl groups being part of weakly basic heterocycles<sup>18</sup>.

Therefore, **28** was hydrogenated with NaBH<sub>3</sub>CN in AcOH<sup>19</sup> (this is superior to NaBH<sub>4</sub> in AcOH<sup>15a</sup>) to yield **29** quantitatively. - **29** was easily hydrogenolyzed to the very labile product **30**, which is rapidly oxidized by air i. a. to compounds showing a positive *van Urk*-reaction.

In the ms of **30** the appearance of an ion at m/z 118 (100% at 70 eV) is surprising. It may correspond to a loss of C<sub>2</sub>H<sub>4</sub> from (M-1)<sup>+</sup>, which is also found in the N-CH<sub>3</sub> derivative

<sup>\*)</sup> This compound was a generous gift of Roussel-Uclaf Company, Paris (cf. Pharm. Ind. 46, 724 (1984)).

31 (see below), in the ms of which it is substantiated by  $m^* = 108.90$ . Up to now we have no sufficing explanation for this process. In 30 the expected benzylic cleavage leads to m/z 132 with 10% rel. int. only.

**30** was N-methylated with HCHO/H<sub>2</sub>/Raney-Ni or with NaBH<sub>4</sub>/HCOOH to **31** in good yields. Unfortunately the anticipated ion from benzylic cleavage  $(M-CH_3)^+$  in the ms of **31** had only 3% rel. int. So, **31** was excluded from CID-MS experiments.

This benzylic cleavage should be favoured by an electron donating increment in the direct neighbourhood (benzylic +  $\alpha$ -cleavage). Therefore, 27 was converted to the carbinol 36 via the acetate 32 (scheme 8).



32 loses acetic acid under EI-conditions even at 12 eV to m/z = 233 (97%). At 70 eV the ion at m/z = 91 gives rise to the base peak. Benzylic cleavage in the side chain leads to m/z = 220 (M - CH<sub>2</sub>O-Ac)<sup>+</sup> with 10% rel. int.

32 is hydrolyzed to 33 which in turn is hydrogenated to 34 by NaBH<sub>3</sub>CN. - Again rupture of the N-benzyl bond overrules the benzylic cleavage in the side chain:  $(M - CH_2OH)^+$  occurs with only 6% rel. int. - In analogy to 29, 34 was debenzylated to 35. 35 is the only crystalline base in this series and, therefore, proved to be rather stable.

**35** loses 45 amu (CH<sub>2</sub>-CH<sub>2</sub>OH) to m/z 118 (89%) directly from M<sup>+</sup> (m\*=85.42). This is the dominant fragmentation pathway of M<sup>+</sup>. In the ms of the corresponding N-methyl derivative **36** (see below) the same fragmentation was observed. This is probably due to a 1.3-H-shift and subsequent bond cleavage at the newly generated sp<sup>3</sup>-C-atom (scheme 9).



Scheme 9

Similar H-migrations have been reported inter alia by  $Gr\ddot{u}tzmacher^{20}$ . **36**, obtained as described for **31**, proved to be unstable. The main decomposition product (van Urk reaction +) was isolated by prep. tlc and identified as the dehydrogenated compound **37**. - Nevertheless, the desired fragment of **36** (M - CH<sub>2</sub>OH)<sup>+</sup> comes up with 28% rel. int.

#### Mass Spectrometry

This section focusses mainly on the formation of ion C  $(R^8=H)$  at m/z 146 (scheme 1).

## A. Tetrahydroisoquinolines

According to our hypothesis<sup>1)</sup> ion C is formed from A by benzylic cleavage at C-1, intramolecular aromatic substitution by the H<sub>3</sub>C-N'-radical, generating a sp<sup>3</sup>-hybridized Catom at the former C-5, and subsequent loss of the "C-5"substituent as a radical (scheme 1). The ms of 5-chloro-1,2,3,4-tetrahydro-2-methylisoquinoline (3) shows ions at m/z 146 (ion C, R<sup>8</sup>=H), the RDA fragment at m/z 138  $(^{35}Cl)$ , and m/z 103 (138 - Cl<sup>'</sup>). The rate of m/z 146 of the total ion current (%  $\Sigma_{40}$ ) is increased from 2.8% (70 eV) to 7.9% at 12 eV. This is in accordance with fragmentations supported by neighbour group effects following fast rearrangements and in contrast to simple bond fission<sup>20,1)</sup>. The same trend is observed with the acetoxy derivative 6: 3.9% at 70 eV, 7.9% at 12 eV. - In the ethoxy-tetrahydroisoquinoline 8 RDA fragmentation produces m/z 148, which is further fragmented: loss of  $CH_3$  leads to m/z 133 (\*119.52), loss of  $C_2H_4$  to m/z 120 (\*97.30), and loss of 44 amu to m/z 104 (\*73.08). M<sup>+-</sup> (m/z 191) loses  $C_2H_5$  to m/z 162 (\*137.40), which ejects stepwise two H to m/z 161 and m/z 160. This fragmentation is also observed in 6-methoxy- $8^{21}$ . Ion C ( $\mathbb{R}^8$ =H) at m/z 146 is formed with 14% rel. int. Again the tendency that formation of this ion is favoured at low activation energies is demonstrated as well by its increasing rate of the total ion current (%  $\Sigma_{40}$ ) at 12 eV - as compared to that at 70 eV - as by the quotient (m/z 146)/RDA which increases from 0.25 (70 eV) to 0.45 (12 eV). - In the bromo compound 2 this quotient is  $\approx 1$  at 12 eV pointing towards a dependence of this cleavage on the dissociation energy of the C-X bond.

The results of the mass spectra of the C-5 substituted tetrahydroisoquinolines concerning the ions at m/z 146 are summarized as follows:

- 1) C-5 substituents are lost even at low activation energies.
- 2) C-5 substituents are very probably lost after rearrangement of  $M^+$ . This is indicated by the increasing rate of the total ion current attributed to ion C (R<sup>8</sup>=H) and by the increase of the quotient (m/z 146)/RDA at 12 eV.
- Tetrahydroisoquinolines with identical substituents either at C-5 or C-8 lose this substituent from C-5 preferentially, as indicated by the rate of m/z 146 of the total ion current<sup>1</sup>.
- 4) The rel. int. of the ions at m/z 146 from the C-5 or C-8 substituted tetrahydroisoquinolines discussed in this and in the preceding paper<sup>1</sup>) are lower than those of analogously substituted tetrahydroisoquinolines with additional electron donating groups at C-5, C-6, and C-8<sup>21</sup>). Probably these substituents promote aromatic radical substitution<sup>22</sup>).

## B. Fragmentation of C-4 substituted 2,3-dihydro-1methylindoles

In the 4-( $\beta$ -hydroxyethyl)indole **36** the fragment ion of highest rel. int. is at m/z 158, resulting from loss of water from (M-1)<sup>+</sup> at m/z 176 (\*141.84). Ion C (R<sup>8</sup>=H) at m/z 146 comes up with 28% rel. int. It loses 2H in one step to m/z 144 as well as by a two step process via m/z 145 as indicated by metastable ions at \*142.03 and \*143.01. m/z 146 splits off CH<sub>3</sub> to m/z 131 (\*117.54).

As expected, the highest rel. int. for m/z 146 was found in the ms of 25 (62%, main fragment). Again loss of 2H, H, and CH<sub>3</sub> are observed from m/z 146. m/z 131 loses H to m/z 130 (\*129.01).

## C. CID-Measurements on m/z 146 (Ion C, $R^8=H$ )

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In order to find out whether the ion population at m/z 146, generated from  $M^+$  of 25 and the C-5 substituted tetrahydroisoquinolines 3, 7, and 8, respectively, are identical or identical mixtures of interconvertible structures, we performed CID-experiments. The theoretical background of CID is discussed inter alia by *Levsen* and *Schwarz*<sup>23)</sup>. CID measurements in the 2. field free region (2. FFR) led to unexpected results (fig. 1):

a) the CID spectrum of m/z 146 from 25 is similar to that of m/z 146 from 3, 8, or 7, but shape and intensity of the signals are not identical.

b) The CID spectra of 3, 7, and 8 are not identical: all the signals of the secondary fragments from m/z 146 of 3 can be found in the spectra of 7 and 8, but in those of 8 there are additional signals at m/z 124/125, and at m/z 133, although of low intensity. Moreover, the signals at m/z 90, m/z 115, and m/z 117 are of different shape.

These results indicate that the population of ions is differently assembled. Therefore, we looked for the precursor ions of m/z 146. The  $B^2/E$  linked scan spectra (1. FFR) revealed:

a) m/z 146 of the alkoxy-derivatives 7 and 8 mainly comes directly from  $M^+$ , but besides that it is generated also from other precursor ions (fig. 2).

This means that m/z 146 is a mixture of ions of different origin and, therefore, of different structure.

b) m/z 146 from the chloro compound 3 originates from  $M^+$  only. Therefore, we assume that the structure of just those m/z 146 ions yielded from  $M^+$  only are identical in 3,



Figure 1: CID - MS (B/E, 1 FFR) of m/z 146-ions from 25, 3, 7, and 8.



Figure 2 MI-MS ( $B^2/E$ , 1 FFR) of m/z 146-ions from 7 and 8.

7, and 8, but this hypothesis can not be proven, because the ions at m/z 146 from 7 and 8 represent isomeric mixtures.

As a consequence we compared the CID B/E linked scan spectra (1. FFR) of the m/z 146 ions from 3, 2, and 6 with the corresponding spectrum of m/z 146 from 25: the patterns of the secondary fragment ions are very similar, but they are not identical. In all these spectra the signals at m/z 77 give rise to the base peak, but in the case of dihydroin-dole 25 there is an additional signal at m/z 72. The signal at m/z 66 from 25 is also found in the acetoxy derivative 6, but not in the halogenated tetrahydro-isoquinolines 2 and 3 (fig. 3 and table 1).

As an explanation we assume that  $M^+$  of 25 is fragmented to m/z 146 on two routes (scheme 10), route a) representing the pathway presumed, route b) being characterized by a cleavage of the C-2/C-3 bond. So, a mixture of isomeric ions forms the signal at m/z 146.



Figure 3

Table 1: CID-MS (B/E, 1 FFR) of m/z 146-ions from 25, 3, 2, and 6 (% R.I / %  $\Sigma$ ).

m/z	25	3 (X = Cl)	2 (X = Br)	$6 (\mathbf{X} = \mathbf{OCCH}_3)$
90	30/5.4	34/4.4	30/5.2	68/9.1
89	52/9.3	62/8.0	59/10.3	98/13.0
88	13/2.3	18/2.3	18/3.1	24/3.1
87	15/2.7	26/3.3	18/3.1	25/3.2
78	37/6.6	29/3.8	29/5.1	41/5.4
77	100/18.0	100/12.9	100/17.4	100/13.2
76	36/6.6	44/5.7	46/8.0	46/6.1
75	32/5.7	51/6.6	41/7.1	48/6.4
74	21/3.7	41/5.3	36/6.3	29/3.8
72	14/2.5	-	-	-
66	13/2.3	-	-	18/2.4
65	28/5.0	28/3.6	23/4.0	38/5.1
64	18/3.2	22/2.8	19/3.2	20/2.7
63	50/8.9	63/8.2	52/9.0	68/9.1
62	25/4.7	39/5.0	33/5.8	32/4.2
53	16/2.9	36/4.6	15/2.6	17/2.2
52	28/5.0	88/11.4	29/5.0	38/5.1
51	29/5.3	81/10.5	27/4.7	31/4.1



 $B^2/E$  measurements of m/z 146 from 6 indicate that this ion is generated from M<sup>+</sup> as well as from m/z 162, which in turn is formed from M<sup>+</sup> by loss of H<sub>2</sub>C=CO.

Up to now we have no sufficient explanation for the difference of the CID-spectra of 2 and 3 although m/z 146 is generated directly from  $M^+$  in both cases. Probably in the C-5 substituted tetrahydroisoquinolines, too, a 1.3-H-shift competes with aromatic substitution (see above), as postulated for the dihydroindoles 35 and 36. Subsequent cleavage of the bond between the newly formed sp<sup>3</sup>-C and its substituent would lead to a species of 146 amu of different structure, probably D (scheme 11).



An ion of this structure should be generated from C-4 substituted tetrahydroisoquinolines: 4-benzoyl-1,2,3,4-tetrahydro-2-methyl-isoquinoline ( $\mathbb{Z}$ )<sup>24)</sup> produces a fragment ion of 146 amu, which was checked by B/E-CID measurements. Its spectrum was very different from those of m/z 146 from 1-( $\alpha$ -hydroxybenzyl)-1,2,3,4-tetrahydro-2-methylisoquinoline ( $\mathbb{Y}$ )<sup>25)</sup> and of 1-( $\alpha$ -chlorobenzyl)-1,2,3,4-tetrahydro-2methylisoquinoline ( $\mathbb{X}$ )<sup>20c)</sup> (scheme 12 and Table 2) but high resolution of m/z 146 from  $\mathbb{Z}$  indicates that this signal



Scheme 12

Table 2: CID-MS (B/E, 1 FFR) of m/z-146 ions from X, Y, Z (% R.I / %  $\Sigma$ ).

m/z	х	Y	Z
128	65/8.1	-	•
127	21/2.6	19/18.4	-
116	100/12.5	100/18.4	-
102	98/12.2	93/17.1	-
101	27/3.4	29/5.4	-
90	46/5.8	48/8.8	54/9.2
89	62/7.8	62/11.3	74/12.4
88	13/1.6	16/2.9	-
78	30/3.8	33/6.1	38/6.4
77	86/10.7	78/14.4	100/16.9
76	34/4.3	42/7.7	55/9.4
75	25/3.1	29/5.3	52/8.7
74	21/2.6	24/4.4	33/5.6
66	15/1.8	-	-
65	26/3.3	26/4.8	41/6.9
64	14/1.7	22/4.0	-
63	44/5.5	42/7.7	64/10.8
62	21/2.6	20/3.7	-
53	15/1.9	-	-
52	20/2.5	-	41/6.9
51	16/2.0	23/4.2	41/6.9
50		20/3.7	-

comprises two non-isomeric ions. So, no conclusions can be drawn from these two experiments. Now we are studying the fragmentation pathways of C-4 substituted tetrahydroisoquinolines in more detail.

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## **Experimental Part**

General remarks:1).

## 5-Nitroisoquinoline<sup>26,27,28)</sup>

5-Nitroisoquinoline was separated from minor quantities of its 8-isomer by repeated crystallizations from benzene and EtOH.- 8-Nitroisoquinoline<sup>29)</sup> was obtained from the mother liquors by LPLC on SiO<sub>2</sub>, diisopropylether as an eluent.

## 2-Methyl-5-nitroisoquinolinium iodide<sup>28)</sup>

1,2,3,4-Tetrahydro-2-methyl-5-nitroisoquinoline<sup>30)</sup>

## 5-Amino-1,2,3,4-tetrahydro-2-methylisoquinoline (1)

1 was obtained as colourless oil which crystallized, m.p.  $72 - 73^{\circ}$ C. After one day the m.p. has changed to 55°C. This value was stable. Both m.ps. are reported:  $50 - 55^{\circ}$ C<sup>30</sup>;  $75^{\circ}$ C<sup>31</sup>.

## 5-Bromo-1,2,3,4-tetrahydro-2-methylisoquinoline (2)

To 0.5 g CuSO<sub>4</sub>.5 H<sub>2</sub>O, dissolved in 2 ml of water by warming, were added 0.31 g NaBr. Under stirring 0.126 g Na<sub>2</sub>SO<sub>3</sub> in 0.5 ml of water were dropped into this solution. After cooling the precipitate was washed with H<sub>2</sub>O, the water phase was decanted, the solid was dissolved in 1 ml of HBr (48%) and cooled to 0°C.- To 260 mg 1, dissolved in 2 ml of HBr (24%) and cooled in an ice bath, are added drop by drop 0.64 ml of 2.5 m NaNO2 solution. After 5 - 10 min the excess of NO2 was destroyed by urea and this solution of the diazonium salt was added to the solution of CuBr mentioned above. Then the mixture was made slightly alkaline and extracted with Et<sub>2</sub>O. After drying and evaporating 183 mg oily material which was purified by column chromatography (cc) (Al<sub>2</sub>O<sub>3</sub>, diisopropyl ether): 140 mg (40%) colourless oil. 2-HCl: mp. 286°C (absol. EtOH).- C10H13BrN·Cl (262.6) calc. C 45.7 H 4.99 N 5.3 found C 45.5 H 4.99 N 5.2.- UV (MeOH):  $\lambda max$  (log  $\epsilon$ ) = 265 (2.48), 204 nm (4.27).- <sup>1</sup>H-NMR:  $\delta$  (ppm) = 243 (s, 3H, NCH<sub>3</sub>), 2.56 - 3.00 (m, 4H, C-3, C-4), 3.52 (s, br., 2H, C-1), 6.91 - 7.09 (m, 2H, ArH, C-7, C-8), 7.25 - 7.49 (m, 1H, ArH, C-6).- MS (12 eV): m/z = 227 (99), 226 (76), 225 (100, M<sup>+</sup>, <sup>79</sup>Br), 224 (76), 184 (2), 182 (2), 147 (5), 146 (32).- (70 eV): m/z = 227 (53), 226 (99), 225 (56, M<sup>+</sup>, <sup>79</sup>Br), 224 (100), 184 (23), 182 (24), 146 (23), 145 (11), 144 (14, \*143.01), 129 (6), 116 (5), 115 (8), 104 (6), 103 (40, \*57.66, \*58.29), 102 (14), 77 (22).

#### 5-Chloro-1,2,3,4-tetrahydro-2-methylisoquinoline (3)

The preparations of CuCl (from 0.175 g NaCl) and of 1-diazonium salt are analogous to the procedure described for 2.-  $CH_2Cl_2$  was used for the extraction of 3 after alkalization: 183 mg (63%) colourless oil.- 3-HCl: m.p. 281°C (absol. EtOH).-  $C_{10}H_{13}$ ClN·Cl (218.1) calcd. C 55.1 H 6.01 N 6.4 found C 54.9 H 6.02 N 6.4.- UV (MeOH):  $\lambda$ max (log  $\varepsilon$ ) = 265 (2.49), 214 nm (3.94).- <sup>1</sup>H-NMR:  $\delta$  (ppm) = 2.42 (s, 3H, NCH<sub>3</sub>), 2.58 - 3.00 (m, 4H, C-3, C-4), 3.52 (s, br., 2H, C-1), 6.84 - 7.30 (m, 3H, ArH).- MS (12 eV): m/z = 183 (32), 182 (28), 181 (100, M<sup>+</sup>, <sup>35</sup>Cl), 180 (64), 146 (15), 138 (4).- (70 eV): m/z = 183 (17), 182 (37), 181 (55, M<sup>+</sup>, <sup>35</sup>Cl), 180 (100), 178 (8), 146 (13), 145 (6), 144 (7), 140 (14), 139 (6), 138 (41), 115 (5), 103 (27), 102 (6).

#### 5-Cyano-1,2,3,4-tetrahydro-2-methylisoquinoline (4)

According to Clarke<sup>2,3)</sup> CuCN was prepared as follows: 0.923 g CuSO<sub>4</sub>·5 H<sub>2</sub>O and 0.240 g NaCl were dissolved by heating in 3 ml of water. To this solution 0.200 g NaHSO3 and 0.130 g NaOH in 3 ml of water were added drop by drop. After cooling the solid was washed, suspended in 2 ml of water and dissolved by 0.480 g NaCN in 1 ml of water. This solution was cooled to 0°C.- 0.360 g 1 were dissolved in about 8 ml 2N H<sub>2</sub>SO<sub>4</sub> and diazotised by 0.9 ml of 2.5 m NaNO2 solution as described for 2. The excess of NO2<sup><sup>-</sup></sup> was destroyed by urea and the solution was made slightly alkaline by Na<sub>2</sub>CO<sub>3</sub>. This alkaline solution was added with cooling to the solution of CuCN (vide supra)<sup>2)</sup> and stirred 1 h at room temp., than 1 h at 50 - 60°C. Extraction with CH<sub>2</sub>Cl<sub>2</sub>, drying, evaporation and purification by cc (Al<sub>2</sub>O<sub>3</sub>/CH<sub>2</sub>Cl<sub>2</sub>) afforded 140 mg (36%) of oily 4. After kugelrohr distillation 4 became solid, mp. 42°C (lit.<sup>32)</sup>: 252°C).- C<sub>11</sub>H<sub>12</sub>N<sub>2</sub> (172.2) calcd. C 76.7 H 7.02 N 16.3 found C 76.7 H 7.01 N 16.2.- IR: 2250 cm<sup>-1</sup>.- UV (MeOH):  $\lambda max$  (log  $\varepsilon$ ) = 289 (3.28), 280 (3.26), 227 nm (3.90).- <sup>1</sup>H-NMR:  $\delta$  (ppm) = 2.46 (s, 3H, NCH<sub>3</sub>), 2.66 - 2.88 (AA'-"t", 2H, C-3), 2.98 - 3.22 (BB'-"t", C-4), 3.58 (s, br., 1H, C-1), 7.17 - 7.59 (m, 3H, ArH).- MS (12 eV):  $m/z = 172 (100, M^+)$ , 171 (56).- (70 eV):  $m/z = 172 (45, M^+)$ , 171 (100), 169 (11), 156 (6), 155 (5), 146 (1), 143 (6), 130 (6), 129 (30), 128 (12), 103 (7), 102 (12), 101 (5).

### 1,2,3,4-Tetrahydro-5-hydroxy-2-methylisoquinoline (5)

3.2 g 1 in 50 ml 2N H<sub>2</sub>SO<sub>4</sub> were diazotized by 1.4 g NaNO<sub>2</sub> in 7 ml of water at 0°C. After 5 min the excess of NO<sub>2</sub><sup>-</sup> was removed by urea and the solution so obtained was dropped into a boiling mixture of 16 g Na<sub>2</sub>SO<sub>4</sub>, 22 g konz. H<sub>2</sub>SO<sub>4</sub> and 12 ml of water (silicon bath, 160°C). After cooling the mixture was alkalized (ph 8 - 9) by Na<sub>2</sub>CO<sub>3</sub>, the precipitate was collected, washed with water and dried: 2.82 g (82%), m.p. 179 - 181°C.- Crude 5 was sublimated (>150°C/0.1 torr) and recrystallized from Et<sub>2</sub>O/EtOH: white crystals, m.p. 182 - 182°C (lit.<sup>30)</sup>: 185 - 187°C; lit.<sup>31)</sup>: 184°C); tlc (Al<sub>2</sub>O<sub>3</sub>, Et<sub>2</sub>O): rf = 0.7.- MS (12 eV): m/z = 163 (100, M<sup>+</sup>), 162 (13), 146 (2, "130.77), -(70 eV): m/z = 163 (86, M<sup>+</sup>), 162 (100, "161.01), 160 (15, "158.02), 147 (9, "133.39), 146 (12, "130.77), 120 (67), 92 (22, "70.53), 91 (54, "90.01).

## 5-Acetoxy-1,2,3,4-tetrahydro-2-methylisoquinoline (6)

0.156 g (0.96 mmole) **5** were acetylated in 10 ml Ac<sub>2</sub>O and 10 drops of pyridine at room temp. for 36 h (tlc control). Conventional work-up, removal of pyridine by kugelrohr distillation and cc (Al<sub>2</sub>O<sub>3</sub>; EtOAc) afforded 0.125 g (64%) of colourless oily **6** (lit.<sup>33)</sup>: oil).- C<sub>12</sub>H<sub>15</sub>NO<sub>2</sub> (205.3) calcd. C 70.2 H 7.37 N 6.8 found C 70.1 H 7.30 N 6.7.- IR: 1770 cm<sup>-1</sup> (ester).-UV (MeOH):  $\lambda$ max (log  $\varepsilon$ ) = 260 (2.51), 208 nm (3.97).- <sup>1</sup>H-NMR:  $\delta$  (ppm) = 2.31 (s, 3H, COCH<sub>3</sub>), 2.43 (s, 3H, NCH<sub>3</sub>), 2.64 - 2.75 (m, 4H, C-3, C-4), 3.56 (s, br., 2H, C-1), 6.80 - 7.27 (m, 3H, ArH).- MS (12 eV): m/z = 205 (100, M<sup>+</sup>), 204 (47), 162 (9), 146 (15), 120 (6).- MS (70 eV): m/z = 205 (66, M<sup>+</sup>), 204 (74, <sup>\*</sup>203.00), 163 (13), 162 (78, <sup>\*</sup>128.65), 160 (13), 147 (5), 146 (20, <sup>\*</sup>103.98), 120 (100), 119 (5), 103 (3), 24 (18).

#### 1,2,3,4-Tetrahydro-5-methoxy-2-methylisoquinoline (7)

For *Rodinov*-methylation and for decomposition of diazotized 1 in MeOH see lit.<sup>6)</sup>.-  $CH_2N_2$  in  $Et_2O$  from 4 g of nitrosomethylurea was added to 0.720 g 5 in 20 ml of absol. MeOH at 0°C. This mixture was worked-up after 24 h at room temp. as usual: 0.396 g (47.3%) colourless oil which was purified by bulb-to-bulb distillation. The distillate solidified: m.p. 35°C.- 7-HCl: m.p. 220°C (lit.<sup>34)</sup>: 221°C).

#### 5-Ethoxy-1,2,3,4-tetrahydro-2-methylisoquinoline (8)

8 was prepared analogously to 7 from 4.68 g ethylnitrosourea<sup>35)</sup> and 0.740 g 5: 0.650 g oil, purified by cc (Al<sub>2</sub>O<sub>3</sub>, diisopropyl ether): 0.370 g

colourless oil (42%).- 8-HCl: m.p. 197°C (EtOH).-  $C_{12}H_{18}$ NO-Cl (227.7) calcd. C 63.3 H 7.97 N 6.1 found C 62.9 H 7.90 N 6.0- MS (12 eV): m/z = 191 (100, M<sup>+</sup>), 190 (39), 162 (4), 148 (15), 146 (7).- (70 eV): m/z = 191 (82, M<sup>+</sup>), 190 (100), 162 (25, <sup>+</sup>137.40), 161 (6), 160 (24, <sup>+</sup>159.01), 149 (7), 148 (58), 147 (6), 146 (14), 133 (10, <sup>+</sup>119.52), 120 (34, <sup>+</sup>97.30), 119 (7), 105 (16), 104 (65, <sup>+</sup>73.08), 92 (12), 91 (27).

#### 2-Methyl-5-nitro-1(2H)-isoquinolinon(12), 5-amino-2-methyl-1(2H)-isoquinolinon(13), and 4-methylaminomethyl-1H-indole(11)

5.3 ml aqueous solution of TiCl<sub>3</sub> (16%) were added under stirring to 320 mg 2-methyl-5-nitroisoquinolinium iodide  $(10)^{28}$  in 4 ml of water<sup>4,5)</sup>. After 7 min stirring at room temp. the mixture was made alkaline with 2N NaOH and then extracted 3 times with MeOH/CH<sub>2</sub>Cl<sub>2</sub> (5 + 95). The org. layer was washed with saturated NaCl solution, dried, and evaporated. The crude material was purified by prep. tlc (Al<sub>2</sub>O<sub>3</sub>, CH<sub>2</sub>Cl<sub>2</sub>). The pertinent zones were extracted with CH<sub>2</sub>Cl<sub>2</sub>.

Fraction A, rf = 0.7, yellow crystals, m.p. 112°C (EtOH). This substance is identical with 12, prepared by oxidation of 2-methyl-5-nitroisoquinolinium iodide; cited m.p.<sup>35)</sup> 116 - 117°C.- MS (12 eV): m/z = 204 (100, M<sup>+</sup>), 161 (20).- (70 eV): m/z = 204 (100, M<sup>+</sup>), 188 (3), 186 (4), 174 (5), 161 (39), 158 (10), 146 (13), 134 (4), 133 (7), 130 (15), 117 (27).

Fraction **B**, rf = 0.3, faint yellow crystals, m.p. 145° (CH<sub>2</sub>Cl<sub>2</sub>), **13**; lit.<sup>36</sup>: 145 - 146°C; lit.<sup>37</sup>): 152 - 153°.

Fraction C was obtained from an analogous experiment with 960 mg 2methyl-5-nitroisoquinolinium iodide (10).- rf = 0.05: 78 mg crude material, purified by prep. tlc (Al<sub>2</sub>O<sub>3</sub>, MeOH/CH<sub>2</sub>Cl<sub>2</sub> 5 + 95). The zone showing a positive reaction with p-dimethylaminobenzaldehyde (*van Urk* reaction) was extracted, the org. material further purified by cc (SiO<sub>2</sub>, MeOH/NH<sub>3</sub> 99 + 1): 4 mg 11 as colourless oil, identified by MS.- MS (12 eV): m/z = 160 (100, M<sup>+</sup>), 159 (19), 131 (22), 130 (14).- (70 eV): m/z = 160 (79), 159 (57), 157 (5), 146 (5), 131 (56, <sup>\*</sup>107.25), 130 (100), 128 (7), 118 (52), 117 (20), 116 (6).

#### 5-Acetamino-2-methyl-1(2H)-isoquinolinone (14)

320 mg 2-methyl-5-nitroisoquinolinium iodide in 4 ml of water were treated with 5.3 ml TiCl<sub>3</sub>-solution as described.- The crude product was acetylated with Ac<sub>2</sub>O and 2 drops of pyridine. Excess of Ac<sub>2</sub>O was destroyed by heating with EtOH. The residue was crystallized from MeOH, m.p. 225°C.- C<sub>12</sub>H<sub>12</sub>N<sub>2</sub>O<sub>2</sub> (216.2).- HR-MS: m/z 216 C<sub>12</sub>H<sub>12</sub>N<sub>2</sub>O<sub>2</sub> calcd. 216.08988 found .08983; m/z 174 C<sub>10</sub>H<sub>10</sub>N<sub>2</sub>O calcd. 174.07931 found .07962.- IR: 3290 (NH); 1665 (amide I); 1545 (amide II) cm<sup>-1</sup>.- UV (MeOH):  $\lambda$ max (log  $\varepsilon$ ) = 328 (3.44), 291 (3.95), 243 (3.29), 217 nm (4.37).- MS (12 eV): m/z = 216 (100, M<sup>+</sup>), 174 (47).- (70 eV): m/z = 216 (59, M<sup>+</sup>), 174 (100), 173 (13), 158 (7), 147 (5), 146 (8), 145 (10), 144 (13), 132 (6), 130 (12), 129 (7), 128 (7), 118 (5), 117 (11), 116 (7), 105 (10), 104 (9), 103 (7).

#### 2-Methyl-3-nitrobenzol-1-methandiol diacetate (16)

16 was prepared from 1,2-dimethyl-3-nitrobenzene (15) with minor modifications<sup>6)</sup> according to  $Askam^{38)}$ .

## 2-Methyl-3-nitro-benzaldehyde dimethylacetal (17)<sup>12)</sup>

## 2-Methyl-3-nitrobenzaldehyde (19)

Slight deviations<sup>6)</sup> from *Askam's* method<sup>38)</sup> led to **19** (97%).- MS (12 eV):  $m/z = 165 (100, M^+)$ , 148 (56), 136 (14), 120 (11), 119 (24), 118 (43), 92 (37), 91 (72).- (70 eV):  $m/z = 165 (34, M^+)$ , 148 (25, \*132.75), 136 (7), 120 (22, \*97.30), 119 (18), 118 (17), 106 (13), 105 (19), 92 (42), 91 (68), 90 (32), 89 (61), 79 (10), 78 (10), 77 (45), 75 (8), 65 (100), 64 (18), 63 (41), 62 (13).

#### 2-(2-Methyl-3-nitrophenyl)-1,3-dioxolane (20)

630 mg (3.82 mmole) 19 in 10 ml CHCl<sub>3</sub> were stirred with 1.24 g (20 mmole) 1,2-dihydroxyethane and 1 ml BF3-Et2O at room temp. After a few min an aqueous phase started to separate. It was bound by Na<sub>2</sub>SO<sub>4</sub>. After 30 min the reaction was complete (tlc;  $SiO_2$ , toluene; rf = 0.35). The org. layer was mixed with ice-cold 2N NaOH and extracted 3 times with CHCl<sub>3</sub>. After washing (H<sub>2</sub>O), drying (K<sub>2</sub>CO<sub>3</sub>), and evaporation in vacuo: 770 mg (96.5%) oily 20, homogenous in tlc. For elementary analysis 20 was sublimated, m.p. 64°C.- C10H11NO4 (209.2) calcd. C 57.4 H 5.30 N 6.7 found C 57.4 H 5.39 N 6.8.- IR: 2910 (CH); 1530; 1365 (NO<sub>2</sub>) cm<sup>-1</sup>.-UV (MeOH):  $\lambda max$  (log  $\epsilon$ ) = 255 (3.60), 207 nm (4.11).- <sup>1</sup>H-NMR:  $\delta$ (ppm) = 2.51 (s, 3H, Ar-CH<sub>3</sub>), 4.01 - 4.23 (m, 4H, O-CH<sub>2</sub>-CH<sub>2</sub>-O), 6.01 (s, 1H, Ar-CH-), 7.23 - 7.46 (ABB'-"t", 1H, ArH), 7.68 - 7.92 (ABB', 2H, ArH).- MS (12 eV): m/z = 209 (100, M<sup>+</sup>), 195 (11), 194 (77), 192 (20), 149 (7), 148 (14), 147 (5), 121 (35), 120 (9), 93 (46), 91 (6), 73 (34).- (70 eV):  $m/z = 209 (16, M^+), 208 (34, 207.00), 194 (20, 180.08), 192 (4, 18$ 176.38), 164 (9), 162 (8), 148 (11), 120 (6), 119 (5), 118 (5), 105 (5), 93 (8), 92 (8), 91 (12), 90 (8), 89 (9), 77 (10), 73 (100).

#### 1H-Indole-4-carbaldehyde (18)

2.0 g (9.51 mmole) 20 in 20 ml of absol. DMF were stirred with 2.0 ml of N,N-dimethylformamide dimethylacetal and 1.6 ml of pyrrolidine under N2 for 3 h at 135°C (bath temp.). Then volatile substances were evaporated in vacuo (90°C, 15 min) and the residue was dissolved in 30 ml of THF/MeOH 1:1. To this solution a suspension of 1.5 g Raney Ni in 50 ml of 2-propanol was added, then 1.6 ml of hydrazine hydrate were added drop by drop. The mixture got warm ( $\approx 50^{\circ}$ C) and N<sub>2</sub> was generated vigorously. When the exothermic reaction had ceased the mixture was kept at 50°C and after 1.5 h again 1.6 ml of hydrazine hydrate were added. After further 3 h at 50°C celite was added and the mixture was filtered with suction. The filtrate was evaporated in vacuo and the residue was purified by cc: 910 mg of 18 contaminated with the corresponding dioxolane 21. After treatment with 0.5 N HCl, alkalization, drying and evaporation in vacuo: 750 mg (54%; lit.<sup>12)</sup>: 33%) 18: colourless oil which crystallized slowly. Recrystallization from CH2Cl2, m.p. 138°C (lit.<sup>12)</sup>: 142°C, lit.<sup>39)</sup>: 138°C).- MS (12 eV):  $m/z 145 (M^+)$ .- (70 eV):  $m/z = 145 (100, M^+)$ , 144 (68, \*143.01), 117 (22), 116 (64, \*93.44), 115 (6), 90 (14, \*69.23), 89 (25, \*68.28), 63 (15), 62 (8).

## E/Z-4-(2-Phenylethenyl)-1H-indole (22)

Na<sup>o</sup> (250 mg) was dissolved in 3.5 ml of absol. MeOH, excess of MeOH was evaporated in vacuo, NaOMe was suspended in absol. Et<sub>2</sub>O under N<sub>2</sub> and stirred for 1 h with 4.95 g of benzyl-triphenylphosphonium bromide  $^{40)}$ (orange colour). - This suspension was stirred with 750 mg (5.17 mmole) 18 at room temp. overnight. - After filtration with suction and washing of the solid (Et<sub>2</sub>O) the etheral layer was evaporated in vacuo and the residue was purified by cc (SiO<sub>2</sub>, toluene, rf = 0.52 and 0.57, van Urk reaction +): 1.05 (93%) colourless oil (E/Z mixture). Addition of a little bit of ether afforded the crystalline E-isomer (rf = 0.52). Recrystallization from petrol ether: colourless crystals, m.p. 130°C.- C<sub>16</sub>H<sub>13</sub>N (219.3) calcd. C 87.6 H 5.98 N 6.4 found C 87.2 H 6.27 N 6.3.- IR: 3400 cm<sup>-1</sup> (NH).- UV (MeOH):  $\lambda \max(\log \varepsilon) = 338 (4.29), 242 (4.20), 212 \text{ nm} (4.38).^{-1}\text{H-NMR}: \delta (\text{ppm}) =$ 6.37 - 7.72 (m, 12H, ArH, olefin. H), 8.05 (s, br., 1H, NH).- MS (12 eV):  $m/z = 219 (M^+)$ .- (70 eV):  $m/z = 219 (100, M^+)$ , 218 (86), 217 (38), 216 (9), 204 (8), 191 (8), 190 (6), 189 (14), 109.5 (14), 109 (13), 108.5 (28), 102 (7), 95.5 (10), 95 (4), 94.5 (8), 94 (3), 92 (11), 91 (15), 89 (5).

#### 4-(2-Phenylethyl-1H-indole (23)

120 mg (0.55 mmoe) 22, dissolved in as little as possible MeOH and a few drops of  $CH_2Cl_2$ , were added in a  $H_2$ -counter current to a pre-hydrogenated suspension of 0.2 g Pd/C 10%.- After 45 min at room temp. and at-

mospheric pressure the theoretical amount of H<sub>2</sub> had been consumed and the reaction was complete (tlc: SiO<sub>2</sub>, toluene, rf = 0.5, *van Urk* reaction +). After filtration, evaporation, and drying: 120 mg colourless oil which formed white crystalls, m.p. 93°C.- C<sub>6</sub>H<sub>15</sub>N (221.3) calcd. C 86.8 H 6.83 N 6.3 found C 86.8 H 6.62 N 6.8.- IR: 3400 cm<sup>-1</sup> (NH).- UV (MeOH): λmax (log ε) = 288 (3.74), 269 (3.95), 217 nm (4.52).- <sup>1</sup>H-NMR: δ (ppm) = 2.88 - 3.36 (m, 4H, Ar-CH<sub>2</sub>-CH<sub>2</sub>-Ph), 6.54 - 6.65 (m, 1H, C-3), 7.07 - 7.34 (m, 9H, ArH), 8.06 (s, br., 1H, NH).- MS (12 eV) m/z = 221 (100, M<sup>+</sup>), 130 (32).- (70 eV): m/z 221 (34, M<sup>+</sup>), 130 (100), 103 (10, \*81.61), 91 (6), 77 (10).

#### 1-Ethyl-4-(2-phenylethyl)-2,3-dihydro-1H-indole (24)

100 mg NaBH<sub>4</sub> were given in portions to 40 mg 23 in 6 ml of absol. acetic acid. After stirring for 1 h at room temp. and 1 h at 60 - 70°C ice was added and the mixture was carefully alkalized by NaOH. After extraction with ether, washing of the org. phase with saturated NaCl, drying (Na<sub>2</sub>SO<sub>4</sub>) and evaporation in vacuo, the crude oil was purified by prep. tlc (SiO<sub>2</sub>, toluene, rf = 0.3, *Dragendorff* reaction +, *van Urk* reaction -): 40 mg (89%) colourless oil.-  $C_{18}H_{21}N$  (251.4).- UV (MeOH):  $\lambda$ max (log  $\varepsilon$ ) = 295 (3.04), 254 (3.49), 207 nm (4.16).- <sup>1</sup>H-NMR:  $\delta$  (ppm) = 1.17 (t, 3H, J = 7 Hz, N-CH<sub>2</sub>-CH<sub>3</sub>), 2.68 - 3.44 (m, 10H, Ar-CH<sub>2</sub>-CH<sub>2</sub>-Ph, Ar-CH<sub>2</sub>-CH<sub>2</sub>-N-CH<sub>2</sub>-CH<sub>3</sub>), 6.32 - 6.45 (AB<u>B</u>'-"d", 1H, C-7), 6.49 - 6.64 (A<u>B</u>B'-"d", 1H, C-5), 6.95 - 7.44 (<u>A</u>BB', 1H, C-6, overlap with m, 5H, ArH).- MS (12 eV): m/z = 251 (100, M<sup>+</sup>), 236 (23).- (70 eV): m/z = 251 (59, M<sup>+</sup>), 250 (5), 236 (100, \*221.90), 160 (5), 159 (5), 158 (14), 146 (5), 145 (26), 144 (11), 130 (11), 105 (6), 91 (6).

#### 2,3-Dihydro-4-(2-phenylethyl)-1H-indole (26)

10 Drops of pyridine-borane-reagent<sup>16)</sup> were added slowly to 50 mg (2.26 mmol) 23 in 2 ml EtOH. Within 30 min 4 ml HCl (10%) were dropped to the mixture until the H2-development ceased. Then the mixture was cooled by ice, alkalized by Na2CO3, and extracted with CH2Cl2. The org. Phase was washed (NaCl solution), dried (K2CO3) and evaporated in vacuo: 50 mg reddish oil, which was purified by cc (SiO<sub>2</sub>, toluene, rf = 0.17; positiv reactions with Ehrlich's and Dragendorff's reagents).- $C_{16}H_{17}N$  (223.1).- HR-MS: m/z 223  $C_{16}H_{17}N$  calcd. 223.13652 found .13609; m/z 132 C<sub>9</sub>H<sub>10</sub>N calc. 132.08132 found .08116.- IR (film): 3380 cm<sup>-1</sup> NH).- UV (MeOH):  $\lambda$ max (log  $\epsilon$ ) = 289 (3.22), 242 (3.69), 211 nm (4.31).- <sup>1</sup>H-NMR:  $\delta$  (ppm) = 2.70 - 3.04 (part of AA'BB'-system, 2H, C-3, overlap by s), 2.84 (s, br., 4H, Ar-CH2-CH2-Ph), 3.25 (s, br., 1H, NH, H/D exchange), 3.38 - 3.65 (part of AA'BB'-system, 2H, C-2), 6.53 (ABB'-"t" from 2 overlapping "d", 2H, C-5 and C-7), 6.98 (ABB'-"t", 1H, C-6), 7.10 -7.44 (m, 5H, ArH).- MS (12 eV): m/z = 223 (100, M<sup>++</sup>), 132 (7).- (70 eV): m/z = 223 (91, M<sup>+</sup>), 222 (8), 221 (5), 165 (18), 133 (12), 132 (100), 130 (53), 119 (7), 118 (27), 117 (22, 103.70), 115 (7), 105 (16), 103 (10), 91 (17), 79 (6), 77 (12).

#### 2,3-Dihydro-1-methyl-4-(2-phenylethyl)-1H-indole (25)

To the solution of 44 mg (0.19 mmole) **26** in 2 ml MeOH 10 drops of an aqueous solution of HCHO (Merck, 35%) were added. After a short time a milky turbidity arose which disappeared within 2 - 3 min. After 15 min stirring at room temp. this solution was poured under H<sub>2</sub>-counter current into a suspension of 100 mg Raney-Ni in MeOH (saturated with H<sub>2</sub>) and was hydrogenated at room temp. and atmospheric pressure (tlc control). After 1 h the reaction was complet (SiO<sub>2</sub>, CH<sub>2</sub>Cl<sub>2</sub>, rf = 0.55, *Dragendorff* reaction +). - The suspension was filtered, the filtrate was evaporated in vacuo, the residue was dissolved in Et<sub>2</sub>O and dried (Na<sub>2</sub>SO<sub>4</sub>). Work-up gave a colourless oil: 43 mg (93%) which decomposes rapidly! - **25**-HCl, prepared by treatment with etheric HCl in absol. acetone, is stable.

**25** (base):  $C_{17}H_{19}N$  (237.3).- <sup>1</sup>H-NMR: (250 MHz)  $\delta$  (ppm) = 2.74 (s, 3H, NCH<sub>3</sub>), 2.78 - 2.92 (m, 6H, C-3 and Ar-CH<sub>2</sub>-CH<sub>2</sub>-Ph), 3.22 - 3.29

(part of AA'BB'-system, 2H, C-2), 6.37 (d, 1H, J = 7.7 Hz, C-7), 6.56 (d, 1H, J = 7.7 Hz, C-5), 7.05 ("t", 1H, J = 7.7 Hz, C-6), 7.16 - 7.31 (m, 5H, ArH).- MS (12 eV):  $m/z = 237 (M^+)$ .- (70 eV):  $m/z = 237 (100, M^+)$ , 236 (20), 146 (62), 145 (24), 144 (44, \*143.01), 132 (18), 131 (15, \*117.54), 130 (10, \*129.01), 105 (20), 91 (9), 77 (7).

**25-**HCl: white crystalls, m.p. 151°C (absol. acetone).-  $C_{17}H_{20}N$ ·Cl (273.8) calcd. C 74.6 H 7.36 N 5.1 found C 73.9 H 7.34 N 5.0.- UV (MeOH):  $\lambda max (\log \epsilon) = 294 (2.83), 252 (3.74), 209 \text{ nm} (4.44).$ 

#### 1-Benzyl-4-ethyl-1H-indole (28)

210 mg 27 (see Theoretical Part) in 10 ml of absol. THF were added dropwise to 55 mg (1.5 mmole) LiAlH<sub>4</sub> in 5 ml of absol. THF at 0°C. After refluxing for 2.5 h under N<sub>2</sub>, the mixture was worked-up by addition of icewater and extraction of the greyish cake with CH<sub>2</sub>Cl<sub>2</sub>. Washing (NaCl solution), drying (Na<sub>2</sub>SO<sub>4</sub>), and evaporation led to a colourless oil, purification by cc (SiO<sub>2</sub>, toluene, rf = 0.8, *van Urk* reaction +): 117 mg (96%) oily material.- C<sub>17</sub>H<sub>17</sub>N (235.3) calcd. C 86.8 H 7.28 N 6.0 found C 86.4 H 6.90 N 6.0.- UV (MeOH):  $\lambda$ max (log  $\varepsilon$ ) = 292 (3.23), 282 (3.30), 271 (3.32), 219 nm (4.01).- <sup>1</sup>H-NMR:  $\delta$  (ppm) = 1.37 (t, 3H, J = 7 Hz, Ar-CH<sub>2</sub>-CH<sub>3</sub>), 2.94 (q, 2H, J = 7 Hz, Ar-CH<sub>2</sub>-CH<sub>3</sub>), 5.24 (s, 2H, N-CH<sub>2</sub>-Ar), 6.56 (d, 1H, J = 3 Hz, C-3), 6.86 - 7.44 (m, 9H, ArH).- MS (12 eV): m/z = 235 (100, M<sup>+</sup>). (70 eV): m/z = 235 (100, M<sup>+</sup>), 234 (6), 221 (16), 220 (82, <sup>\*</sup>205.95), 204 (9), 205 (15), 203 (7), 145 (5), 144 (8), 143 (5), 142 (5), 132 (6), 117 (10), 115 (8), 104 (9), 91 (94).

#### 1-Benzyl-4-ethyl-2,3-dihydro-1H-indole (29)

To 140 mg **28** in 7 ml of absol. acetic acid were added in portions 120 mg NaBH<sub>3</sub>CN. Then the mixture was stirred under N<sub>2</sub> for 6 h at room temp. - After cooling by ice, alkalization with NaOH, and extraction with Et<sub>2</sub>O, the org. layer was washed (NaCl solution), dried (K<sub>2</sub>CO<sub>3</sub>), and evaporated: 135 mg colourless oil, homogenous in tlc (SiO<sub>2</sub>, toluene, rf = 0.7; *Dragendorff* reaction +).- C<sub>17</sub>H<sub>19</sub>N (237.2) calcd. C 86.0 H 8.07 N 5.9 found C 86.1 H 8.35 N 6.1.- UV (MeOH):  $\lambda$ max (log  $\varepsilon$ ) = 291 sh (3.50), 254 (4.04), 209 nm (4.56).- <sup>1</sup>H-NMR: 1.19 (t, 3H, J = 7 Hz, Ar-CH<sub>2</sub>-CH<sub>3</sub>), 2.56 (q, 2H, J = 7 Hz, Ar-CH<sub>2</sub>-CH<sub>3</sub>), 2.77 - 3.03 (AA'BB', 2H, C-3), 3.19 - 3.45 (AA'BB', 2H, C-2), 4.22 (s, 2H, N-CH<sub>2</sub>-Ar), 6.31 - 6.43 (AB<u>B</u>'-"d", 1H, C-7), 6.47 - 6.63 (A<u>B</u>B'-"d", 1H, C-5), 6.92 - 7.14 (<u>A</u>BB'-"t", 1H, C-6), 7.16 - 7.46 (m, 5H, ArH).- MS (12 eV): m/z = 237 (100, M<sup>+</sup>), 236 (7), 161 (8), 160 (6), 147 (7), 146 (8).- (70 eV): m/z = 237 (100, M<sup>+</sup>), 236 (27), 235 (7), 220 (6), 160 (57), 146 (42), 130 (20), 118 (30), 117 (15), 91 (100), 90 (17).

## 4-Ethyl-2,3-dihydro-1H-indole (30)

125 mg 29 were hydrogenolyzed as described for the conversion of 34 to 35 (see below): 64 mg (83%) colourless labile oil which was further processed immediately as such.- UV (MeOH):  $\lambda max$  (log  $\varepsilon$ ) = 286 (2.87), 240 (3.32), 206 nm (4.06).-

#### 4-Ethyl-2,3-dihydro-1-methyl-1H-indole (31)

a) for N-methylation with HCHO/Raney-Ni see preparation of 25.

b) 20 mg (0.14 mmole) **30** were dissolved in 2 ml of absol. HCOOH and stirred with 50 mg NaBH<sub>4</sub> at first at room temp., then at 40°C. - After addition of ice and NaOH, extraction with Et<sub>2</sub>O, washing of the org. phase with NaCl solution, drying (Na<sub>2</sub>SO<sub>4</sub>), and evaporation: 18 mg crude material, which was purified by micro-cc (*Pasteur* pipette; SiO<sub>2</sub>, CH<sub>2</sub>Cl<sub>2</sub>, rf = 0.7, *Dragendorff* reaction +): colourless oil (14 mg; 64%).- C<sub>11</sub>H<sub>15</sub>N (161.3) calcd. C 81.9 H 9.38 N 8.7 found C 82.1 H 9.50 N 8.5.- <sup>1</sup>H-NMR (250 MHz):  $\delta$  (ppm) = 1.19 (t, J = 7.6 Hz, 3H, Ar-CH<sub>2</sub>-CH<sub>3</sub>), 2.54 (q, J = 7.6 Hz, 2H, Ar-CH<sub>2</sub>-CH<sub>3</sub>), 2.75 (s, 3H, NCH<sub>3</sub>), 2.86 - 2.93 (AA'BB', 2H, C-3), 3.26 - 3.33 (AA'BB', 2H, C-2), 6.35 ("d", 1H, C-7), 6.55 ("d", 1H, C-5), 7.05 ("t", 1H, C-6).- MS (12 eV): m/z = 161 (M<sup>+</sup>).- (70 eV): m/z = 161

(84, M<sup>+</sup>), 160 (100, <sup>\*</sup>159.01), 146 (3), 145 (6), 144 (11), 132 (28, <sup>\*</sup>108.90), 131 (20), 130 (11), 117 (9, <sup>\*</sup>103.70).

#### 4-(2-Acetoxyethyl)-1-benzyl-1H-indole (32)

100 mg (0.25 mmole) **27** in 15 ml glacial acetic acid were boiled with 150 mg freshly molten and powdered sodium acetate. After cooling, addition of ice and NaOH, **32** was extracted with Et<sub>2</sub>O. Usual work-up and purification by cc (SiO<sub>2</sub>, CH<sub>2</sub>Cl<sub>2</sub>, rf = 0.5, *van Urk* reaction +) gave 69 mg (96%) oily **32**.- C<sub>19</sub>H<sub>19</sub>NO<sub>2</sub> (293.4) calcd. C 77.8 H 6.53 N 4.8 found C 77.7 H 6.65 N 4.5.- IR (film): 1740 cm<sup>-1</sup> (C=O).- <sup>1</sup>H-NMR:  $\delta$  (ppm) = 2.03 (s, 3H, COCH<sub>3</sub>), 3.21 (t, J = 7 Hz, 2H, Ar-CH<sub>2</sub>-CH<sub>2</sub>O), 4.41 (t, J = 7 Hz, 2H, Ar-CH<sub>2</sub>-CH<sub>2</sub>O), 5.28 (s, 2H, N-CH<sub>2</sub>-Ar), 6.60 (d, J = 4 Hz, 1H, C-3), 6.85 - 7.41 (m, 9H, ArH).- MS (12 eV): m/z = 293 (180, M<sup>+</sup>), 234 (6), 233 (97), 172 (26), 155 (12).- (70 eV): m/z = 293 (18, M<sup>+</sup>), 234 (13), 233 (60), 220 (10), 172 (20), 155 (25), 123 (10), 90 (11), 91 (100).

#### 1-Benzyl-4-(2-hydroxyethyl)-1H-indole (33)

160 mg (0.55 mmole) **32** in 2.5 ml EtOH were refluxed for 2 h with 65 mg NaOH in 5 ml 50% EtOH. Usual work-up and cc (SiO<sub>2</sub>, CH<sub>2</sub>Cl<sub>2</sub>, rf = 0.25, *van Urk* reaction +) afforded a colourless oil which crystallized in the refrigerator: 123 mg (90%), m.p. 50 - 51°C.- C<sub>17</sub>H<sub>17</sub>NO (251.3) calcd. C 81.2 H 6.82 N 5.6 found C 80.6 H 6.67 N 5.5.- IR (film): 3360 cm<sup>-1</sup> (OH).-UV (MeOH):λmax (log  $\varepsilon$ ) = 292 (3.80), 271 (3.92), 219 nm (4.57).- <sup>1</sup>H-NMR: δ (ppm) = 1.65 (s, 1H, OH, H/D exchange), 3.15 (t, J = 7 Hz, 2H, Ar-CH<sub>2</sub>-CH<sub>2</sub>OH), 3.96 (t, J = 7 Hz, 2H, Ar-CH<sub>2</sub>-CH<sub>2</sub>OH), 5.28 (s, 2H, N-CH<sub>2</sub>-Ar), 6.59 (d, J = 4 Hz, 1H, C-3), 6.85 - 7.47 (m, 9H, ArH).- MS (12 eV): m/z = 251 (100, M<sup>+</sup>), 220 (10).- (70 eV): m/z = 251 (72, M<sup>+</sup>), 221 (22), 220 (100, <sup>\*</sup>192.83), 92 (15), 91 (83), 86 (27), 84 (42).

#### 1-Benzyl-4-(2-hydroxyethyl)-2,3-dihydro-1H-indole (34)

215 mg (8.6 mmole) **33** in 15 ml of glacial acetic acid were slowly mixed with 250 mg NaBH<sub>3</sub>CN and then stirred under N<sub>2</sub> at room temp. The colour of the solution changed from originally deep red to yellow. After decomposition with ice and NaOH, extraction (Et<sub>2</sub>O), washing (NaCl solution), drying (K<sub>2</sub>CO<sub>3</sub>), and evaporation 200 mg (92%) colourless oil (decomposition on SiO<sub>2</sub> with CH<sub>2</sub>Cl<sub>2</sub>!).- IR (film): 3350 cm<sup>-1</sup> (OH).- UV (MeOH):  $\lambda$ max (log  $\varepsilon$ ) = 290 (3.25), 257 (3.81), 209 nm (4.39).- <sup>1</sup>H-NMR:  $\delta$  (ppm) = 1.71 (s, 1H, OH, H/D exchange), 2.78 (t, J = 7 Hz, 2H, Ar-CH<sub>2</sub>-CH<sub>2</sub>OH, overlap with AA'BB'), 2.80 - 3.49 (AA'BB', 4H, C-2 and C-3), 3.81 (t, J = 7 Hz, 2H, Ar-CH<sub>2</sub>-CH<sub>2</sub>OH), 4.25 (s, 2H, N-CH<sub>2</sub>-Ar), 6.33 - 6.48 (ABB'-"d", 1H, C-7), 6.48 - 6.61 (ABB'-"d", 1H, C-5), 6.94 - 7.16 (ABB'-"d", 1H, C-6), 7.17 - 7.47 (m, 5H, ArH).- MS (12 eV): m/z = 253 (100, M<sup>+</sup>), 251 (5), 176 (3), 144 (3).- (70 eV): m/z = 253 (100, M<sup>+</sup>), 251 (5), 176 (3), 117 (11), 115 (9), 103 (6), 92 (17), 91 (99).

#### 4-(2-Hydroxyethyl)-2,3-dihydro-1H-indole (35)

50 mg (0.2 mmole) **34** in 5 ml MeOH/CH<sub>2</sub>Cl<sub>2</sub> (9:1) were hydrogenolyzed over 150 mg Pd/C (10%) in 5 ml MeOH at room temp. and atmospheric pressure (tlc control). - After work-up and cc (SiO<sub>2</sub>, rf = 0.32, *Ehrlich's* reagent +) white crystals from Et<sub>2</sub>O, 19 mg (60%), m.p. 80°C.-C<sub>10</sub>H<sub>13</sub>NO (163.2) calcd. C 73.6 H 8.03 N 8.6 found C 73.2 H 8.12 N 8.3.-IR: 3250; 3170 cm<sup>-1</sup>.- UV (MeOH):  $\lambda$ max (log  $\varepsilon$ ) = 290 (3.35), 241 (3.79), 207 nm (4.48).- <sup>1</sup>H-NMR (250 MHz): 2.79 (t, J = 6.7 Hz, 2H, Ar-CH<sub>2</sub>-CH<sub>2</sub>OH), 3.00 ("t", 2H, C-3), 3.55 ("t", 2H, C-2), 3.82 (t, J = 6.7 Hz, 2H, Ar-CH<sub>2</sub>-CH<sub>2</sub>OH), 6.50 - 6.59 ("t", 2 overlapping d, 2H, C-5 and C-7), 6.98 ("t", 1H, C-6).- MS (12 eV): m/z = 163 (100, M<sup>+</sup>), 118 (3).- (70 eV): m/z = 163 (100, M<sup>+</sup>), 146 (7), 145 (6), 144 (45), 133 (12), 132 (53), 131 (15), 130 (55, \*128.03, \*129.01), 120 (9), 119 (14), 118 (83, \*85.42), 117 (38, \*103.70), 116 (10), 105 (9), 103 (12), 91 (11), 77 (20).

#### 2,3-Dihydro-4-(2-hydroxyethyl)-1-methyl-1H-indole (36)

a) 15 mg (0.09 mmole) 35 in 1 ml HCOOH were stirred with 40 mg NaBH<sub>4</sub> for 2 h at room temp. - After addition of ice and NaOH 36 was extracted with  $Et_2O$ . The org. layer was washed with 2N NaOH and saturated NaCl solution. Evaporation afforded 14 mg (86%) colourless oil.

b) 30 mg (0.18 mmol) 36 in 2 ml MeOH were stirred with 0.5 ml HCHO (35% solution) for 15 min at room temp. This solution was treated with Raney-Ni, saturated with H<sub>2</sub>, for 1 h at room temp. and normal pressure. Usual work-up led to 28 mg (86%) colourless oil of 36. 36 is very labil. Even after 1 day under N2 in the refrigerator the sample had become yellow. For analytical purposes (see MS-Section) it has to be purified immediately before use by prep. tlc (SiO<sub>2</sub>, EtOAc, rf = 0.6, Dragendorff reaction +).-  $C_{11}H_{15}NO$  (177.2).- IR (film): 3340 cm<sup>-1</sup> (OH).- UV (MeOH):  $\lambda max$  $(\log \varepsilon) = 296 (3.27), 253 (3.81), 209 \text{ nm} (4.35).^{-1}\text{H-NMR: } \delta (\text{ppm}) = 1.70$ (s, br., 1H, OH, H/D-exchange), 2.74 (s, 3H, NCH<sub>3</sub>), 2.68 - 3.12 (m, 4H, part of AA'BB'-system, C-3 and Ar-CH2-CH2OH), 3.19 - 3.55 (part of AA'BB'-system, 2H, C-2), 3.81 (t, J = 7 Hz, 2H, CH<sub>2</sub>OH), 6.31 - 6.47 (ABB'-"d", 1H, C-7), 6.47 - 6.67 (ABB'-"d", 1H, C-5), 6.96 - 7.18 (ABB'-"t", 1H, C-6).- MS (12 eV): m/z = 177 (100, M<sup>+</sup>).- (70 eV): m/z = 177(100, M<sup>+</sup>), 176 (20, <sup>\*</sup>175.01), 175 (6), 160 (6), 159 (11), 158 (74, <sup>\*</sup>141.84), 147 (9), 146 (28), 145 (14), 144 (42, \*142.03, \*143.01), 143 (19), 133 (8), 132 (47, \*98.44), 131 (17, \*117.54), 130 (14), 117 (14), 115 (10), 103 (8), 91 (8), 77 (10).

#### 4-(2-Hydroxyethyl)-1-methyl-1H-indole (37)

**37** was obtained by prep. tlc purification of **36** (vide supra).  $C_{11}H_{13}NO$  (175.2).- <sup>1</sup>H-NMR:  $\delta$  (ppm) = 1.57 (s, br., 1H, OH), 3.24 (t, J = 7 Hz, 2H, CH<sub>2</sub>-CH<sub>2</sub>OH), 3.78 (s, 3H, NCH<sub>3</sub>), 3.97 (t, J = 7 Hz, 2H, CH<sub>2</sub>-CH<sub>2</sub>OH), 6.56 (d, J = 3 Hz, 1H, C-3), 6.91 - 7.34 (m, 4H, ArH).- MS (12 eV): m/z = 175 (100, M<sup>+</sup>), 145 (8), 144 (19).- (70 eV): m/z = 175 (35, M<sup>+</sup>), 158 (1), 145 (15), 144 (100), 143 (9), 115 (8), 103 (6), 91 (12).

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