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# Cleavage of 1-Benzyltetrahydroisoquinolines to Secondary Amines via Urethanes

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# Cleavage of 1-Benzyltetrahydroisoquinolines to Secondary Amines via Urethanes

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2,2,2-Trichloroethyl chloroformate and benzyl chloroformate cleave 1-benzyl-1,2,3,4-tetrahydro-2-methylisoquinolines of type **1** to yield tertiary stilbene urethanes of type **2** which are easily reduced or hydrogenolyzed to secondary amines. 6′-(Hydroxymethyl)-laudanosine **(4)** is converted by these reagents to the isochroman urethanes **11** and **12** which are split to yield the secondary amine **8** without the isochroman moiety being attacked.

**Spaltung von 1-Benzyl-tetrahydroisochinolinen über Urethane zu sekundären Aminen**

Chlorameisensäure-2,2,2-trichlorethylester bzw. Chlorameisensäurebenzylester spalten 1-Benzyl-1,2,3,4-tetrahydro-2-methylisochinoline vom Typ **1** zu tertiären Stilben-Urethanen vom Typ **2**, die unter milden Bedingungen reduktiv bzw. hydrogenolytisch zu sekundären Aminen gespalten werden. 6′-Hydroxymethyllaudanosin **(4)** reagiert mit diesen Reagentien zu den Isochroman-Urethanen **11** bzw. **12**, die ohne Angriff am Isochromanring zum sekundären Amin **8** umgesetzt werden.

*Gadamer* and *Knoch*[1)] have found that ethyl chloroformate transforms 1-benzyl-1,2,3,4-tetrahydro-2-methylisoquinolines (e.g. **1**) easily into stilbene-urethanes (e. g. **2**). Unfortunately the CO–OEt–moiety is fixed very strongly to the N-atom[1,2)], so that the synthetic value of this reagent is diminished. *v. Bruchhausen* and *Knabe*[3)] have overcome this disadvantage by $LiAlH_4$-reduction of the urethane to the N,N-dimethyl function[3)] (e. g. **3**). Moreover ethyl chloroformate degradation of 6′-hydroxymethyllaudanosine **(4)** leads to the 3-phenylisochroman ring system **5**, and the $LiAlH_4$ reduction of the N-methylcarbamate function in **5** was easily achieved to produce the N,N-dimethylamine derivative **6**[4)].

+) Herrn Professor *Brockmann,* Göttingen, zum 80. Geburtstag freundlichst gewidmet.

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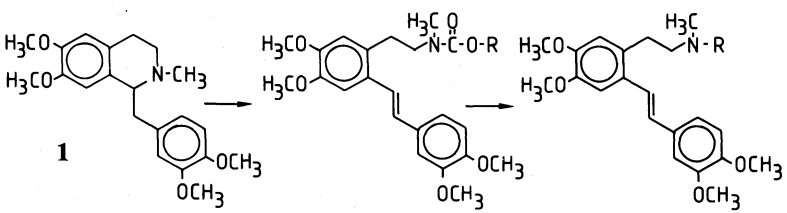
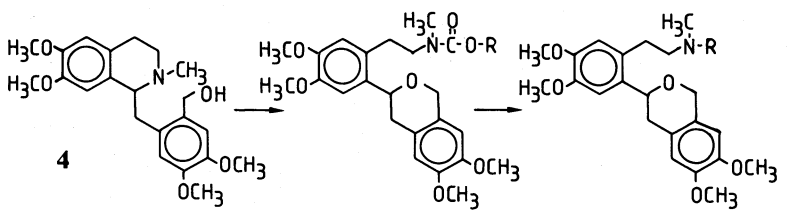
The corresponding N-monomethylamines **7** and **8** can serve as versatile intermediates in alkaloid synthesis. The syntheses of **7** and **8** from the carbamates **2** and **5** have not yet been reported. Hydrolyses of carbamates with strong acids[5] or strong bases[6] are commonly known, but the isochroman ring in **5** may not be compatible with these hydrolytic conditions. So it seemed worthwhile to obtain urethanes which can be split under mild conditions: 2,2,2-trichloroethyl chloroformate (TEC) and benzyl chloroformate (BC) enabled us to prepare the secondary amines **7** and **8**. The trichloroethoxycarbonyl moiety[7,8] is well known as a protecting group of alcohols and amines in alkaloids and steroids. It is particulary useful for compounds containing structures sensitive to acidic or basic conditions on account of its facile removal by zinc/acetic acid reduction. The reaction of laudanosine **(1)** with TEC affords the 2,2,2-trichloroethyl-N-methylcarbamate **9**. Upon reduction of **9** with zinc dust in glacial acetic acid at room temp., the N-methylamine **7** was obtained. The reaction of 6′-hydroxymethyllaudanosine **(4)** with TEC produced the corresponding carbamate **11**, which was reduced to the N-methylamine **8**.

The benzyloxycarbonyl group is also widely used as protecting group in organic syntheses[9–18], the removal of this function can be achieved by Pd-catalyzed hydrogenolysis. When laudanosine **(1)** and 6′-hydroxymethyllaudanosine **(4)** were reacted with BC, the corresponding benzyl carbamates **10** and **12** were formed. While the hydrogenolysis of the benzylcarbamate **12** yielded the secondary amine **8**, the benzylcarbamte **10** was transformed into dihydro-**7** = **13** by concomitant hydrogenation of the stilbene double bond. **7** and **8** were reacted with ethyl chloroformate to the N-methylcarbamates **2** and **5**, so confirming the structure assignments.



**1** **2**: R = $C_2H_5$ **3**: R = $CH_3$
**9**: R = $CH_2$-$CCl_3$ **7**: R = H
**10**: R = $CH_2$-Ø **13**: dihydro-*7*



**4** **5**: R = $C_2H_5$ **6**: R= $CH_3$
**11**: R = $CH_2$-$CCl_3$ **8**: R= H
**12**: R = $CH_2$-Ø

## Experimental Part

*M.P.:* Thomas-Hoover melting point apparatus, uncorr. – *$^1$H-NMR spectra:* Varian EM 360 A (60 MHz) in $CDCl_3$, TMS as int. stand. – *IR spectra:* Perkin-Elmer 735 B spectrophotometer, KBr pellets. – *UV-spectra:* Uvikon 810 spectrophotometer (Kontron). – *Elementary Analyses:* Perkin-Elmer 240 C,H,N-analyzer. – All compound were checked by tlc (chloroform-acetone-methanol 2 : 2 : 1, v/v), using Baker-flex flexible sheets 7.5 × 2.5 cm. – The UV-spectra correspond to those of similar compounds: isochromans:[4], stilbenes:[3].

### Isochromans

*6'-Hydroxymethyllaudanosine* **(4)** was prepared as reported[19,20].

*3-[2'-(β-N-2,2,2-Trichloroethoxycarbonyl-N-methyl-aminoethyl)-4',5'-dimethoxyphenyl]-6,7-dimethoxyisochroman* **(11)**

A mixture of 1.2 g (3 mmol) **4** in 14 ml $CHCl_3$-ether 1 : 1 and 14 ml 15 % KOH and 1.4 ml (10 mmol) 2,2,2-trichloroethyl chloroformate (TEC) was reacted under reflux for 2 h. Another 14 ml 15 % KOH and 1.4 ml TEC were added and 2 h later, the excess of TEC was destroyed by heating with 7 ml 15 % KOH. After 1 h the org. layer was separated and concentrated to give a yellow oily residue which was crystallized with ether: 1.4 g (85 %), mp. 142°, Rf = 0.79. $C_{25}H_{30}Cl_3NO_7$ (562.7) Calcd. C 53.3 H 5.33 N 2.5 Found C 53.7 H 5.22 N 2.4. IR: 1715 $cm^{-1}$ (CO). $^1$H-NMR: δ (ppm) = 2.70–4.06 (m; 6H, $-CH_2-$), 2.93 (s; 3H, $-NCH_3$), 3.87 (s;, 12H, $-OCH_3$), 4.68 (t; J = 5 Hz, 1H, –O–CH–), 4.70 (s; 2H, $-CH_2-CCl_3$), 4.93 (s; 2H, $-O-CH_2-$), 6.56, 6.61, 6.70 and 7.03 (4 × s; 4H, aromatic Hs).

*3-[2'-(β-N-Benzyloxycarbonyl-N-methyl-aminoethyl)-4',5'-dimethoxyphenyl]-6,7-dimethoxyisochroman* **(12)**

**12** was prepared by the procedure described above, 1.2 g (3 mmol) **4** and 1.4 ml (10 mmol) benzyl chloroformate (BC) were used: 1.4 g (91 %), mp. 143° from ether, Rf = 0.77. $C_{30}H_{35}NO_7$ (521.5) Calcd. C 69.1 H 6.71 N 2.7 Found C 68.6 H 6.65 N 2.6. IR: 1710 $cm^{-1}$ (CO). $^1$H-NMR: δ (ppm) = 2.67–4.00 (m; 6H, $-CH_2-$), 2.87 (s; 3H, $-NCH_3$), 3.80 (s; 3H, $-OCH_3$), 3.86 (s; 9H, $-OCH_3$), 4.80 (t; J = 5 Hz, 1H, –O–CH–), 4.87 (s; 2H, $-O-CH_2-$), 5.05 (s; 2H, $-CH_2$-phenyl), 6.56, 6.63 and 7.06 (3 × s; 4H, aromatic Hs), 7.30 (s; 5H, $-C_6H_5$).

*3-[2'-(β-N-Methylaminoethyl)-4',5'-dimethoxyphenyl]-6,7-dimethoxyisochroman* **(8)**

1) A solution of 1.1 g (2 mmol) **11** in 5 ml dioxan and 10 ml glacial acetic acid and 1.0 g zinc dust (zinc was activated according to[21]) was stirred for 4 h at room temp. After removal of zinc, the filtrate was made strongly alkaline with conc. NaOH and extracted with $CHCl_3$. The organic layer was concentrated to give an oily residue, which was dissolved in ether. To this solution conc. HCl was added dropwise until the salt formation was completed. The solution of **8**-HCl in little water was made alkaline to give **8**: 0.5 g (65 %), mp. 115° from ether, Rf = 0.14. $C_{22}H_{29}NO_5$ (387.5) Calcd. C 68.2 H 7.48 N 3.6 Found C 67.8 H 7.67 N 3.5. IR: 2750–3050 $cm^{-1}$ (NH). $^1$H-NMR: δ (ppm) = 1.79 (s; 1H, –NH), 2.44 (s; 3H, $-NCH_3$), 2.60–3.23 (m; 6H, $-CH_2-$), 3.91 (s; 12H, $-OCH_3$), 4.87 (t; J = 5Hz, 1H, –O–CH–), 4.97 (s; 2H, $-O-CH_2-$), 6.60, 6.67, 6.77 and 7.13 (4 × s; 4H, aromatic Hs).

2) A suspension of 0.52 g (1 mmol) **12** and 0.4 g Pd/C (10 %) (Aldrich Chemical Co.) in 50 ml EtOH was shaken with $H_2$ for 1 h at atomospheric pressure. After removal of Pd/C, the filtrate was concentrated and the residue treated with conc. HCl as described above. Usual work-up (see above) gave 0.24 g **8** (62 %).

*3-[2'-(β-N-Ethoxycarbonyl-N-methyl-aminoethyl)-4',5'-dimethoxyphenyl]-6,7-dimethoxyisochroman* **(5)**

0.2 g (0.5 mmol) **8** in 5 ml $CHCl_3$ were added to 0.1 ml ethyl chloroformate and treated with 4–5 drops triethylamine. The mixture was stirred for a few min at room temp. and concentrated, usual work-up led to **5** in 95 % yield, which was crystallized with ether. Its physical data correspond to those of an authentic sample[20].

## Stilbenes

*2-(β-N-2,2,2-Trichloroethoxycarbonyl-N-methyl-aminoethyl)-4,5,3',4'-tetramethoxystilbene* **(9)**

1.07 g (3 mmol) (±) **1** (Aldrich Chemical Co.) in 16 ml $CHCl_3$-ether 1 : 1 were stirred with 16 ml 15 % KOH and 1.4 ml (10 mmol) TEC on the steam bath for 2 h; the organic layer was concentrated to give a yellow oily residue which was crystallized with ether: 1.2 g (75 %), mp. 135–136°, Rf = 0.7. $C_{24}H_{28}Cl_3NO_6$ (532.9) Calcd. C 54.1 H 5.25 N 2.6 Found C 54.2 H 5.27 N 2.8. IR: 1710 $cm^{-1}$ (CO). $^1$H-NMR: δ (ppm) = 2.93 (s; 3H, $-NCH_3$), 2.56–4.13 (m; 4H, $-CH_2-$), 3.93 (s; 6H, $-OCH_3$), 3.97 (s; 3H, $-OCH_3$), 4.00 (s; 3H, $-OCH_3$), 4.67 (s; 2H, $-CH_2-CCl_3$)*), 6.57–7.43 (m; 7H, aromatic and vinyl Hs).

*2-(β-N-Benzyloxycarbonyl-N-methyl-aminoethyl)-4,5,3',4'-tetramethoxystilbene* **(10)**

**10** was prepared by the procedure and work-up described above, 1.07 g (3 mmol) **1** and 1.4 ml (10 mmol) BC were used: 1.0 g (71 %), mp. 126–127° from ether, Rf = 0.69. $C_{29}H_{33}NO_6$ (491.5) Calcd. C 70.9 H 6.71 N 2.9 Found C 71.0 H 6.92 N 2.9. IR: 1680 $cm^{-1}$ (CO). $^1$H-NMR: δ (ppm) = 2.87 (s; 3H, $-NCH_3$), 2.57–4.10 (m; 4H, $-CH_2-$), 3.83 (s; 3H, $-OCH_3$), 3.90 (s; 6H, $-OCH_3$), 3.96 (s; 3H, $-OCH_3$), 5.07 (s; 2H, $-CH_2$-phenyl), 6.40–7.50 (m; 7H, aromatic and vinyl Hs), 7.33 (s; 5H, $-C_6H_5$).

*2-(β-N-Methylaminoethyl)-4,5,3',4'-tetramethoxystilbene* **(7)**

0.53 g (1 mmol) **9** in 3 ml dioxane and 5 ml glacial acetic acid were stirred with 0.5 g zinc dust and worked up as described for **11** to **8**: 0.23 g (65 %), mp. 106° from ether, Rf = 0.13. $C_{21}H_{27}NO_4$ (357.5) Calcd. C 70.5 H 7.55 N 3.9 Found C 70.4 H 7.32 N 3.9. IR: 2750–3000 $cm^{-1}$ (NH). $^1$H-NMR: δ (ppm) = 2.47 (s; 3H, $-NCH_3$), 2.70–3.20 (m; 4H, $-CH_2-$), 3.00 (s; 1H, –NH), 3.93 (s; 6H, $-OCH_3$), 3.97 (s; 6H, $-OCH_3$), 6.63–7.30 (m; 7H, aromatic and vinyl Hs).

*1-[2'-(β-N-Methylaminoethyl)-4',5'-dimethoxyphenyl]-2-(3'',4''-dimethoxyphenyl)-ethane* **(13)**

0.49 g (1 mmol) **10** in 40 ml $CHCl_3$ were hydrogenated with 0.4 g 10 % Pd/C at room temp. under atmospheric pressure for 6 h (absorption 45 ml, calcd. 44.8 ml). After filtration the solution was concentrated i. vac., the oily residue was crystallized with ether. 0.26 g (71 %), mp. 184°, Rf = 0.6. **13**-p-Nitrobenzoylamide was prepared according to Schotten-Baumann, mp. 125° (EtOH). $C_{28}H_{32}N_2O_7$ (508.6) Calcd. C 66.1 H 6.35 N 5.5 Found C 66.1 H 6.23 N 5.5. Data of **13:** MS (70 eV): m/z 359 ($M^{+\cdot}$, 6 %), 316 [$M^{+\cdot}$-($CH_3$–N=$CH_2$), 56 %, *278.15], 165 [316 – ($\cdot CH_2$–$C_6H_3(OCH_3)_2$), 100

*) Note added in proof: The 90 MHz-NMR-spectrum of **9** shows **two** s for $-CH_2-CCl_3$ at δ = 4.62 ppm and 4.68 ppm. Heating up to 85° leads to one s at δ = 4.57 ppm, after cooling the sample shows two s at the original positions again. The origin of this doubling is unknown, this phenomenon is not observed in dihydro-**9**.

%, *86.16], 151 ($^{+}CH_2$–$C_6H_3(OCH_3)_2$, 31 %), 44 ($H_3C$–$^{+}NH$=$CH_2$, 78 %). IR: 2700–3200 $cm^{-1}$ (NH). $^1$H-NMR: δ (ppm) = 2.66 (s; 3H, –$NCH_3$), 2.66–3.40 (m; 4H, –$CH_2$–), 2.90 (s; 4H, Ar–$CH_2$–$CH_2$–Ar), 3.90 (s; 6H, –$OCH_3$), 3.93 (s; 3H, –$OCH_3$), 3.96 (s; 3H, –$OCH_3$), 6.80 and 6.88 (2 × s; 5H, aromatic Hs), 9.43 (broad; 1H, –NH). UV (methanol) λmax (log ε): 212 (4.26), 2.30 (4.22), 280 nm (3.80).

*2-(β-N-Ethoxycarbonyl-N-methyl-aminoethyl)-4,5,3',4'-tetramethoxystilbene* **(2)**

0.18 g (0.5 mmol) **7** in 5 ml $CHCl_3$ were added to 0.1 ml ethyl chloroformate and treated with a few drops of triethylamine. According to the procedure used in the synthesis of **5** from **8**, **2** was obtained in 98 % yield and identified by comparison of its physical data with those of an authentic sample[1].

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