SONDERDRUCK
Scientia Pharmaceutica, 51. Jg., Heft 2, Seite 179–183 (1983)

Sci. Pharm. **51**,179–183 (1983)

3-Phenylisochromans and 2-Phenylbenzofurans from 1-Benzyl-tetrahydroisoquinolines: Tertiary Alcohol- and Phenol-Groups as Nucleophiles

R. Ambros, S. Prior and **W. Wiegrebe**

Institute of Pharmacy, University of Regensburg, FRG

(Received March 28, 1983)

Ethyl chloroformate (ECF) and the 1-benzyl-tetrahydroisoquinoline with a α-hydroxy-α-methylethyl-group at C-2' **5** react to a 1,1-dimethyl-3-phenylisochroman **6**. Under identical conditions the C-2'-OH-substituted 1-benzyl-tetrahydroisoquinoline **7** affords the stilbene **13** and a 2-phenylbenzofuran **14.**

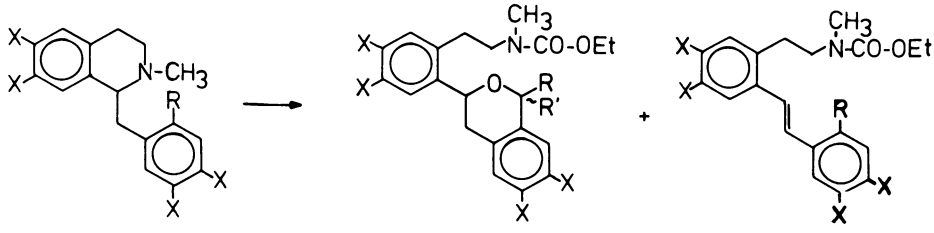
(Keywords: Ethyl chloroformate, 3-phenylisochromans, 2-phenylbenzofurans, intramolecular nucleophilic substitution.)

3-Phenylisochromane und 2-Phenylbenzofurane aus 1-Benzyl-tetrahydroisochinolinen: tertiäre Alkohol- bzw. Phenol-Gruppen als Nucleophile.

Chlorameisensäureethylester und das 1-Benzyl-tetrahydroisochinolin mit einer α-Hydroxy-α-methylethyl-Gruppe an C-2' (**5**) reagieren zu einem 1,1-Dimethyl-3-phenylisochroman **6.** Unter gleichen Bedingungen bilden sich aus dem C-2'-OH-substituierten 1-Benzyl-tetrahydroisochinolin **7** das Stilben **13** und das 2-Phenylbenzofuran **14.**

Introduction

In 1968 we have found that 1-(2-α-hydroxyalkyl-benzyl)-1,2,3,4-tetrahydro-2-methylisoquinolines (e. q. **1**) are converted to 3-phenylisochromans (e. g. **2**) by ethyl chloroformate (ECF) under basic conditions[1]. The structure of **2** was confirmed by independent synthesis[2], stereochemical experiments (**3** → **4**) revealed an S_Ni-mechanism with inversion at C-1 of the benzyl-tetrahydroisoquinoline[3]. These experiments have also shown that primary alcohols (e. g. **3**) lead to results analogous to those of secondary alcohols[3]. Other O-nucleophiles used in this reaction are deprotonated aldehyde hydrates[4] and the carboxylat ion[5], leading to 1-hydroxy-3-phenylisochromans and 1-oxo-derivatives, respectively.



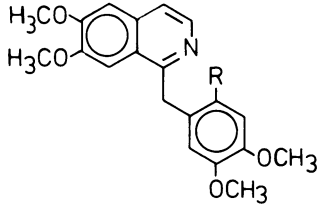
	R
1	$CHOH-CH_3$
3	CH_2OH
5	$C(CH_3)_2-OH$
7	OH

	R	R'
2	CH_3	H
4	H	H
6	CH_3	CH_3

	R
11	$CHOH-CH_3$
12	CH_2OH
	—
13	O-CO-OEt

X = OCH_3

This paper deals with the ECF-reactions of the tertiary alcohol **5** and the phenol **7**.

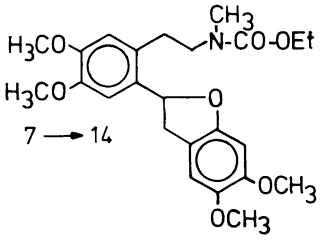


	R
8	H
9	$CO-CH_3$
10	$C(CH_3)_2-OH$

Results and Discussion

5 has been prepared from 6'-acetopapaverine (**9**) (obtained from papaverine (**8**) via coralynsulfoacetate[6,7]) which was methylated by CH_3Li to **10.** Quaternisation of **10** produced **10**-N-methyliodide, which was reduced by $NaBH_4$ to **5.** The reaction of **5** with ECF under standard conditions[1] led to **6.** The MS-fragmentation pattern of the 3-phenylisochromans is well known[2]: the dominating course is a retro-Diels-Alder-fragmentation of the tetrahydropyran-system, explaining the base peak m/z = 192 of **6.** Minor fragmentation processes which are described for **2**[2] with 1 to 7 % rel. intensity can't be found in the MS of **6** or are of even lower intensity.

The ECF-reactions of **1** and **3** produce the stilbene urethans **11** and **12** as minor products, but there was no stilbene fluorescence observed during the pertinent reaction of **5.** Whilst this behaviour remains to be explained, it became evident by comparing the reactions of **3** and **7** under standard conditions[1] that the ring strain of the benzofuran system contributes to the formation of the stilbene: the phenol **7** leads mainly to the stilbene **13,** whilst the benzofuran **14** became the minor product.



Experimental Part

Apparatus[3]:

1-(2-Acetyl-4,5-dimethoxybenzyl)-6,7-dimethoxyisoquinoline ("6'-Acetopapaverine") (**9**) was prepared from papaverine (**8**) according to Schneider[6,7].

1-[2-(α-Hydroxy-α-methylethyl)-4,5-dimethoxybenzyl]-6,7-dimethoxyisoquinoline (10)

3.2 g (8.4 mmol) **9** in 70 ml absol. tetrahydrofuran were cooled to −10° by ice/NaCl. 4.51 ml of a 5% solution of CH_3Li (10 mmol) were added dropwise. The mixture was allowed to reach room temp. and poured into ice water. The alkaline medium was extracted with CH_2Cl_2, the oily residue was purified on SiO_2 (70–230 mesh ASTM) with CH_3CN as solvent and crystallized from ether: 1.6 g (47%). mp. 163° (decomposition).

$C_{23}H_{27}NO_5$ calc.: 397.18891

found: 397.18760 (MS, high resolution).

IR (KBr): 3400 cm^{-1} (OH).

MS (in brackets: relative intensities for 70 eV/12 eV):

m/z = 397 (M^+; 1%/–), 396 (3%/6%), 395 (3%/16%), 383 (5%/3%), 382 (9%/8%), 381 (–/4%), 380 (4%/11%), 379 (5%/8%), 377 (–/3%), 365 (5%/3%), 364 (17%/10%), 340 (9%/5%), 339 (27%/24%), 338 (100%/100%)[9], 324 (6%/–), 323 (4%/–), 322 (9%/–), 308 (4%/–), 307 (4%/–), 208 (–/3%), 207 (–/7%), 206 (–/6%), 205 (–/4%), 203 (–/4%).

^{1}H-NMR: δ (ppm) = 1.73 (s; 6H, $-CH_3$), 3.66 (s; 3H, $-OCH_3$), 3.88 (s; 3H, $-OCH_3$), 4.07 (s; 3H, $-OCH_3$), 4.12 (s; 3H, $-OCH_3$), 4.9 (s; 2H, $-CH_2$), 6.67 (s; 1H, ArH), 6.97 (s; 1H, ArH), 7.15 (s; 1H, ArH), 7.75 (s; 1H, ArH), 7.42, 8.24 (AB; J = 6 Hz, 2H, ArH).

UV (methanol): λ max (log ε) = 239 (4.77), 270 (3.71), 314 (3.47), 326 nm (3.55).

Quaternization of 10 to 10-CH_3I

0.4 g (1 mmol) **10** were refluxed for 150 min. with 5 ml CH_3I. – The precipitate was washed with ether: 0.5 g (94%), mp. 132°.

Reduction of 10-CH_3J to 1-[2-(α-Hydroxy-α-methylethyl)-4,5-dimethoxybenzyl]-1,2,3,4-tetrahydro-5,6-dimethoxy-2-methyl-isoquinoline (5)

To a suspension of 0.4 g (0.7 mmol) **10**-CH_3J in 15 ml CH_3OH/H_2O 1:1 37 mg $NaBH_4$ were added in small portions. – The alkaline solution was concentrated i. vac., the residue was suspended in water and extracted with CH_2Cl_2. After drying

(Na_2SO_4) and removal of the solvent the residue crystallized from ether: 242 mg (79 %), mp. 91°.

$C_{24}H_{33}NO_5$ (415.5)

IR (KBr): 3400 cm^{-1} (OH).

MS (FD): m/z = 415 (M^+).

MS (9 eV): no M^+; m/z = 206 (3,4-dihydro-6,7-dimethoxy-2-methylisoquinolinium-ion).

^{1}H-NMR: δ (ppm) = 1.56 (s; 3H, $-CH_3$), 1.63 (s; 3H, $-CH_3$), 2.33 (s; 3H, N-CH_3), 2.38 – 3.55 (m; 7H, $-CH_2-$, –CHN), 3.85 (s; 3H, $-OCH_3$), 3.98 (s; 3H, $-OCH_3$, 4.03 (s; 3H, $-OCH_3$), 4.06 (s; 3H, $-OCH_3$), 6.62 (s; 1H, ArH), 6.77 (s; 1H, ArH), 6.90 (s; 1H, ArH), 7.12 (s; 1H, ArH).

UV (methanol): λ max (log ε) = 234 (sh, 4.20), 283 nm (3.78).

Reaction of 5 with ECF to 1,1-Dimethyl-3-[2-(β-N-ethoxycarbonyl-N-methyl-aminoethyl)-4,5-dimethoxyphenyl]-6,7-dimethoxyisochroman (6)

0.2 g (4.8 mmol) **5** in 3 ml $CHCl_3$-ether (1 : 1 v/v) were stirred with 3 ml KOH (15 %) and 0.4 ml ECF for 2 hrs. This procedure was repeated[1], then the excess of ECF was destroyed by stirring with 1.5 ml KOH (15 %) for 30 min. The organic layer was separated, the aqueous layer was extracted with ether. Drying (Na_2SO_4) and evaporation gave crystals which were recrystallized from ether: 182 mg (78 %), mp. 157.5°.

$C_{27}N_{37}NO_7$ (487.6) calc.: C 66.4 H 7.58
found: C 66.1 H 7.54

IR (KBr): 1695 cm^{-1} (N-CO).

MS: m/z = 487 (M^+; 14 %), 357 (3 %), 294 (5 %), 222 (8 %), 207 (10 %), 192 (100 %), 179 (5 %), 177 (8 %, *163.17).

^{1}H-NMR: δ (ppm) = 1.2 (t; J = 7 Hz, 3H, $-CH_2\underline{CH_3}$), 1.67 (s, 3H, $-CH_3$), 1.71 (s; 3H, $-CH_3$), 2.98 (s; 3H, $-NCH_3$), 2.68 – 4.33 (m; 8H, $-CH_2-$, $-\underline{CH_2}CH_3$), 4.0 (s; 3H, $-OCH_3$), 4.06 (s; 3H, $-OCH_3$), 4.08 (s; 3H, $-OCH_3$), 4.10 (s; 3H, $-OCH_3$), 5.27 (dd; J_1 = 11 Hz, J_2 = 3.5 Hz; 1H, –HC–O), 6.83 (s; 1H, ArH), 6.9 (s; 1H, ArH), 7.38 (s; 1H, ArH), 7.55 (s; 1H, ArH).

Reaction of 1-(2-Hydroxy-4,5-dimethoxybenzyl)-1,2,3,4-tetrahydro-6,7-dimethoxy-2-methylisoquinoline (7) to 2-(β-N-Ethoxycarbonyl-N-methyl-aminoethyl)-2'-ethoxycarbonyloxy-4,5-4',5'-tetramethoxystilbene (13) and 2-[2-(β-N-Ethoxycarbonyl-N-methyl-aminoethyl)-4,5-dimethoxyphenyl]-2,3-dihydro-5,6-dimethoxybenzofuran (14)

0.75 g (2 mmol) **7**[8] were treated with ECF as described above. – The oily mixture of products was separated on SiO_2 using ether as solvent.

Fraction 1: colourless oil, crystallizing from ether: 0.28 g (27 %), mp. 139° (**13**).

$C_{27}H_{39}NO_9$ (517.6) calc.: C 62.6 H 6.82,
found: C 62.5 H 6.57

IR (KBr): 1680 (N-CO), 1750 cm^{-1} (C-CO).

MS: m/z = 517 (M^+; 100 %), 414 (39 %, *331.52), 342 (17 %), 341 (35 %, *280.87), 278 (23 %).

^{1}H-NMR: δ (ppm) = 1.21 (t; J = 7 Hz, 3H, $-CH_2-C\underline{H}_3$), 1.40 (t; J = 7 Hz, 3H, $-CH_2-C\underline{H}_3$), 2.91 (s; 3H, $-NCH_3$), 2.98 – 4.13 (m; 4H, $-CH_2-$), 3.94 (s; 6H, $-OCH_3$), 3.97 (s; 3H, $-OCH_3$), 4.38 (q; J = 7 Hz, 2H, $-C\underline{H}_2-CH_3$), 6.75 (s; 2H, ArH), 6.82 – 7.50 (m; 2H, vinylic-H), 7.11 (s; 1H, ArH), 7.19 (s; 1H, ArH).

UV (methanol): λ max (log ε) = 242 (sh; 3.98), 296 (4.03), 334 nm (4.15).

Fraction 2 of the separation mentioned above needs rechromatographing on SiO_2 with CH_2Cl_2/ethyl acetate 1:1 (v/v):
0.1 g (11 %) of oily **14.**

$C_{24}H_{31}NO_7$ (445.5)
IR (film): 1690 cm^{-1} (CO).
MS: m/z = 445 (M^+; 100 %), 342 (59 %), 329 (29 %), 324 (25 %), 298 (16 %), 279 (27 %), 175 (27 %), 167 (20 %), 116 (27 %).

^{1}H-NMR: δ (ppm) = 1.24 (t; J = 7 Hz, 3H, $-CH_2-C\underline{H}_3$), 2.74 – 4.07 (m; 6H, $-CH_2-$), 2.91 (s; 3H, $-NCH_3$), 3.88 (s; 6H, $-OCH_3$), 3.91 (s; 6H, $-OCH_3$), 4.17 (q; J = 7 Hz, 2H, $-C\underline{H}_2-CH_3$), 6.02 (t; J = 8 Hz, 1H, –O–CH–), 6.58 (s; 1H, ArH), 6.77 (s; 1H, ArH), 6.87 (s; 1H, ArH), 7.09 (s; 1H, ArH).

UV (methanol): λ max (log ε) = 232 (4.09), 288 (3.18), 300 nm (sh, 3.75).

References

[1] W. Wiegrebe: Arch. Pharm. (Weinheim) **301,** 672 (1968).
[2] W. Wiegrebe, J. Fricke, H. Budzikiewicz and L. Pohl: Tetrahedron **28,** 2849 (1972).
[3] W. Wiegrebe, S. Prior and K. K. Mayer: Arch. Pharm. (Weinheim) **315,** 262 (1982).
[4] M. Shamma, A. S. Rothenberg, G. S. Jayatilake and S. F. Hussain: Tetrahedron **34,** 635 (1978).
[5] W. Wiegrebe and S. Prior: Chimia **32,** 256 (1978).
[6] W. Schneider and K. Schroeter: Ber. Dtsch. Chem. Ges. **53,** 1459 (1920); W. Schneider and O. Boeger: Ibid. **54,** 2021 (1921).
[7] W. Wiegrebe: Dtsch. Apoth.-Ztg. **106,** 1546 (1966).
[8] P. Wiriyachitra and M. P. Cava: J. Org. Chem. **42,** 2274 (1977).
[9] The loss of 59 mu ($\dot{C}(CH_3)_2OH$) may be caused by the formation of a tetramethoxy-indolo[2,1-α]isoquinolinium-ion: K. K. Mayer, G. Stöber and W. Wiegrebe: Arch. Pharm. (Weinheim), in press.

Author's address: Prof. Dr. Wolfgang Wiegrebe, Institute of Pharmacy, University of Regensburg, Universitätsstraße 31, D-8400 Regensburg, BRD.

Eigentümer, Herausgeber und Verleger: Österreichische Apotheker-Verlagsgesellschaft m.b.H., 1094 Wien, Spitalgasse 31, Telefon 42 35 88 Serie – Schriftleitung: Univ.-Prof. Mag. pharm. Dr. Kurt Jentzsch, Institut für Pharmakognosie, 1090 Wien, Währinger Straße 25. – Hersteller: Agens-Werk Geyer + Reisser, 1051 Wien, Arbeitergasse 1–7.