Monatshefte für Chemie 129, 967–974 (1998)

Monatshefte für Chemie
Chemical Monthly

Printed in Austria

Benzoanalogous Congeners of Streptazolin

Martin Kratzel* and **Alexander Weigl**

Institute of Pharmaceutical Chemistry, University of Vienna, A-1090 Vienna, Austria

Summary. Streptazolin, a unique natural compound with antibiotic and antifungal activities, is based on a hexahydro-1*H*-1-pyrindine system containing an internal urethane unit and an exocyclic ethylidene side chain. The diene system, which represents an important structural feature for biological activity, is also responsible for the propensity of streptazolin to polymerize upon concentration from organic solutions. The formal annulation of an aromatic ring under preservation (and prolongation) of the diene system leads to congeners with enhanced stability but reduced antibiotic activity.

Keywords. Streptazolin; Benzoanalogues; Antibiotic activity; Antifungal activity.

Benzoanaloga des Streptazolins

Zusammenfassung. Das antibiotisch und antifungal wirksame Streptazolin besitzt eine für einen Naturstoff außergewöhnliche Struktur. Diese basiert auf einem Hexahydro-1*H*-1-pyrindin-System, das als weitere Strukturmerkmale eine endocyclische Urethangruppierung und eine exocyclische Ethylidenfunktionalität aufweist. Das für die biologische Aktivität essentielle Diensystem zeichnet jedoch auch für die Polymerisationsneigung der Verbindung verantwortlich, die zu unwirksamen Polymeren führt. Die formale Anellierung eines Aromaten unter Erhalt (und Verlängerung) des Diensystem liefert Derivate mit erhöhter Stabilität, aber reduzierter antibiotischer Wirkung.

Introduction

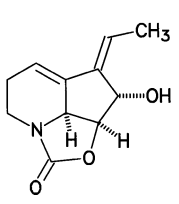
Streptazolin (**1**), isolated from cultures of *Streptomyces viridochromogenes*, exhibits antimicrobial and antifungal activities [1, 2]. Due to the diene system, it tends to polymerize which not only causes difficulties during isolation and purification but also results in a loss of activity. This property seems to be the reason for the fact that pharmacological data of this unique antibiotic have not yet been published.

Enhanced stability and solubility can be achieved by conversion of streptazolin and dihydrostreptazolin to their glucopyranosides [3]. We strive for the same aim but try to realize it by means of the total synthesis of congeners which contain the structural features apparently essential for biological activity and provide a simpler access. We have recently reported on the synthesis of monocyclic mimicries

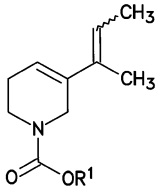
* Corresponding author

(**2**, $R^1 =$ alkyl) of streptazolin which have satisfactory stability, however, limited antibiotic activity [4].

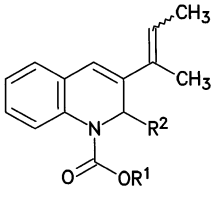
In the following we describe the synthesis of bicyclic congeners of the general structure **3** ($R^1 =$ alkyl, $R^2 =$ H, alkyl) which represent benzoanalogous compounds in comparison with our monocyclic derivatives **2** and also with streptazolin **1** itself, considering a scission of the cyclopentane ring.



1



2

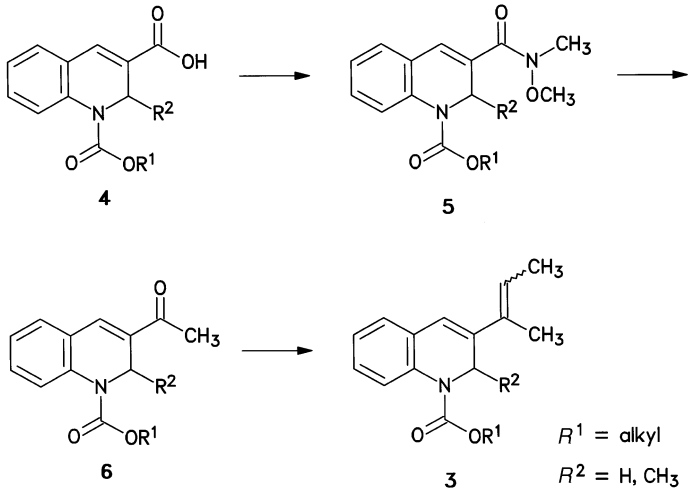


3

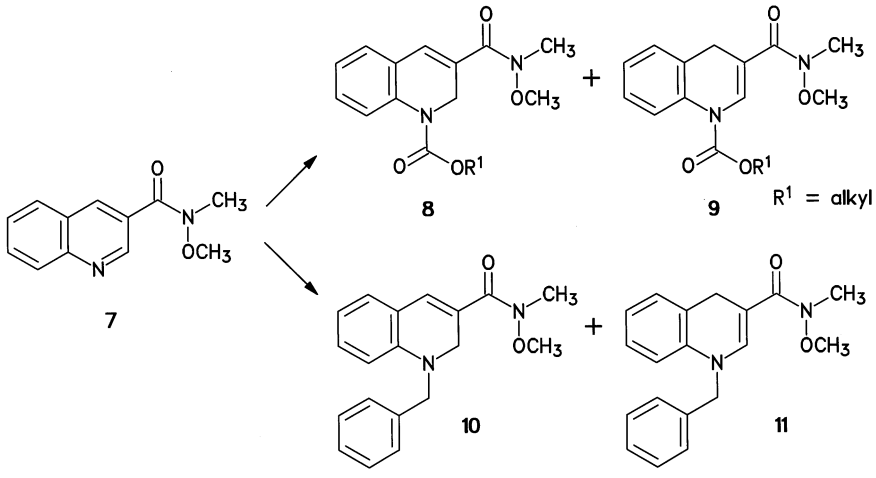
Results and Discussion

The synthesis of **3** was devised according to our strategy to construct the exocyclic double bond starting from a carboxylic acid (**4**) *via* the *Weinreb* amide **5** which can be converted to ketone **6** by reductive alkylation [5]. The last step would consist in a *Wittig* reaction yielding the diene **3** (Scheme 1).

In a previous work, we have extensively examined the reduction of 3-substituted pyridine derivatives using sodium borohydride in the presence of chloroformates [6]. However, application of these experimental conditions to 3-substituted quinolines, *e.g.* **7**, resulted in only low yields of an isomeric mixture of reduction products **8** and **9** which was dominated by the 1,4-dihydro product **9**. Quaternization of **7** by *N*-alkylation *e.g.* *N*-benzylation, followed by reduction using sodium borohydride also provided a mixture of 1,2-(**10**) and 1,4-dihydroquinolines (**11**) which subsequently isomerized, contrary to the reduction



Scheme 1

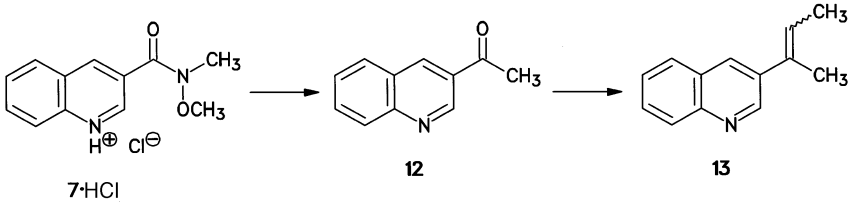


Scheme 2

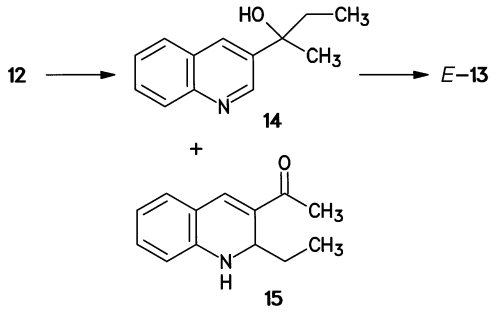
of comparable compounds described in Ref. [7], to the 1,4-dihydro product **11** (Scheme 2).

Derivatives with alkyl substituents at the 2-position made the synthesis of the demanded 1,2-dihydroquinolines more applicable, since **6** ($R^2 = \mathrm{Me}$) should be readily accessible (without formation of the unwanted 1,4-dihydro isomer) by reductive alkylation of amide **7** using an excess of CH_3Li. Interestingly, **7** · HCl gave the fully aromatic ketone **12** in acceptable yields after addition of triethylamine without formation of the 1,2-dihydro compound under the same reaction conditions (Scheme 3). *Wittig* reaction of **12** with ethyl-triphenyl-phosphonium bromide yielded a mixture of *E*- and *Z*-**13**. Contrary to the case of the monocyclic dienes **2** we were able to separate the isomers. The assignment of *E*/*Z*-isomers could be solved using ^{1}H, ^{1}H NOE experiments. Upon irradiation of H-2 of *E*-**13**, a response at H-2′ and at the 1′-methyl group could be observed. Moreover, by irradiation of H-2′ the signals of H-2 and obviously of the 2′-methyl group were affected. However, in *Z*-**13** a significant NOE between H-2 and both methyl groups of the double bond was detected but no influence of H-2′ on H-2. This is most probably due to the conformational equilibrium of the alkenyl moiety.

To prepare **13** by an alternative approach, the tertiary alcohol **14** was prepared by reaction of **12** with ethylmagnesium bromide. The side reaction yielding the 1,2-dihydroquinoline **15** with preserved carbonyl moiety (which is a homologous 1,2-dihydroquinoline and therefore also applicable for our purposes) could not be



Scheme 3



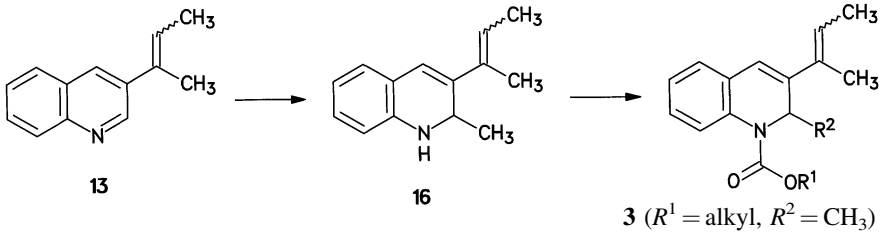
Scheme 4

prevented. It is remarkable that dehydration of **14**, which required heating in 6 *N* HCl, exclusively afforded *E*-**13** whose ethylidene stereochemistry corresponds to the configuration of natural streptazolin (Scheme 4).

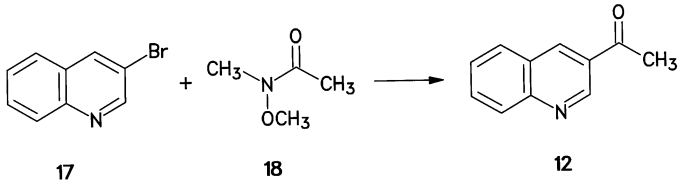
The reaction sequence was terminated by the generation of the 1,2-dihydroquinoline **16** which was obtained by treatment of **13** with CH_3Li. In the last step, the secondary amine **16** was acylated by various chloroformates to generate molecules with different pharmacokinetic properties (Scheme 5).

The target compounds **3**, which were also produced with various substituents at the exocyclic double bond, proved to be stable in comparison with streptazolin. The antibiotic activity, which was at first evaluated for **3** (with $R^1 = \text{Et}$ and $R^2 = \text{Me}$) against *Staphylococcus aureus*, *coagulase-negative Staphylococcus* and *E. coli*, including the antifungal activity against *Candida albicans*, is considerably lower compared to the activity of the monocyclic derivatives **2**.

In conclusion, this work demonstrates that the prolongation of the diene system by an aromatic ring leads to compounds with satisfactory stability, but reduced antibiotic activity. However, the outlined strategy for the synthesis of compounds **3** with the opportunity for numerous variations of the molecular structure will



Scheme 5



Scheme 6

probably offer the access to compounds with optimized activity; this topic is currently under investigation. In that way, the separation of both steps of reductive alkylation (**7** · HCl → **12**, **13** → **16**) allows to introduce different substituents at C-2 and C-1′. Moreover, the synthesis of ketone **12** as a key compound can be economized by bromo-lithium exchange of **17** and reaction with **18** (Scheme 6). The yields are satisfactory, and the use of quinoline-3-carboxylic acid, a conventional but expensive starting compound for the synthesis of **7**, can be avoided.

Experimental

Melting points were taken on a Kofler hot stage apparatus and are uncorrected. Solvents and common reagents were obtained commercially and used as received, tetrahydrofuran and diethyl ether were dried by distillation from sodium/benzophenone. Elementary analyses were performed by Mag. *J. Theiner*, Institute of Physical Chemistry, University of Vienna. Their result were in satisfactory agreement with the calculated values. IR spectra were recorded as KBr pellets using a Perkin Elmer model 298 spectrophotometer. NMR spectra were determined on Bruker AC 80 and Varian Unity-plus 300 instruments. All substances were measured in $CDCl_3$. ^{1}H NMR spectra were recorded with $(CH_3)_4Si$ as the internal reference, the chemical shifts of the ^{13}C NMR spectra are given in ppm relative to the resonance of $CDCl_3$ (77.0 ppm). Mass spectra were recorded on a Hewlett Packard GC-MS equipment (HP-5890A, HP-5970C, HP-59970). Flash chromatography was performed on Merck silica gel 60.

N. Methoxy-N-methyl quinoline-3-carboxamide (**7**; $C_{12}H_{12}N_2O_2$)

Method A. 1.7 g quinoline-3-carboxylic acid (10 mmol) were heated under reflux with 15 ml $SOCl_2$ for 30 min. Excess $SOCl_2$ was removed under reduced pressure, and the residual acid chloride was redissolved twice in toluene and evaporated. The resulting brown residue was dissolved in 50 ml CH_2Cl_2, cooled to 0 °C, and treated with 1.1 g *N*-methoxy-*N*-methylhydroxylamine hydrochloride (11 mmol). After addition of 1.85 g pyridine (22 mmol), the cooling bath was removed and the solution was stirred for 2 h at room temperature. After washing the mixture with water, saturated aqueous $NaHCO_3$, and brine, the organic layer was separated, dried (Na_2SO_4), and the solvent was removed under reduced pressure to give a red oil. Purification by flash chromatography (ethyl acetate) afforded 1.5 g **7** (70%) as an oil.

^{1}H NMR (80 MHz): $\delta = 9.23$ (1H, d, $J = 2.4$ Hz, 2-H), 8.58 (1H, d, $J = 2.4$ Hz, 4-H), 8.25–7.50 (4H, m, arom. H), 3.57 (3H, s, OCH_3), 3.45 (3H, s, NCH_3) ppm; ^{13}C NMR (20.12 MHz): $\delta = 176.2$ (C = O), 149.0 (2-C), 148.3 (8a-C), 136.5 (4-C), 130.6, 128.9, 126.9, 128.4 (arom. CH), 126.8 (3-C), 126.6 (4a-C), 61.0 (OCH_3), 33.1 (NCH_3) ppm; IR (**7** · HCl, KBr): $\nu = 1650$, 1630 cm^{-1}; MS: $m/z = 216$ (M^+).

Reduction of N-methoxy-N-methyl quinoline-3-carboxamide (**7**) *with sodium borohydride after 1-benzylation* (**10**, **11**; $C_{19}H_{20}N_2O_2$)

2.16 g **7** (10 mmol) were heated to 130 °C with 1.3 ml benzyl bromide (11 mmol) without solvent until crystals were formed (about 20 min). The residue was recrystallized from ethanol and then dissolved in a mixture of methanol (10 ml) and water (15 ml). After cooling to 0 °C, 420 mg $NaBH_4$ (12 mmol) were added in small portions. The cooling was removed, the mixture was stirred for 30 min and finally extracted with 3 × 10 ml diethyl ether. The combined organic extracts were washed with brine, dried (Na_2SO_4), and evaporated *in vacuo*. Flash chromatography (diethyl ether) afforded a mixture of **10** and **11** (2.6 g, 85%) which gradually isomerized to **11**.

Yellow oil; ^{1}H NMR (80 MHz): $\delta = 7.48–6.62$ (10H, m, arom. H, 2-H), 4.78 (2H, s, benzyl-H), 3.92 (2H, s, 4-H), 3.64 (3H, s, OCH_3), 3.26 (3H, s, NCH_3) ppm; IR (KBr): $\nu = 1650\,cm^{-1}$; MS: $m/z = 308$ (M^+).

3-Acetyl-quinoline (**12**; $C_{11}H_9NO$)

Method A, starting from **7**. To a solution of 505 mg **7** · HCl (2 mmol) in dry *THF* 0.3 ml (2 mmol) triethylamine were added. The mixture was cooled to −78°C. Then, 2.5 ml CH_3Li (1.6 *M*; 4 mmol) were slowly added. After 1 h at −78°C the solution was allowed to warm to room temperature. The reaction was quenched with saturated aqueous ammonium chloride and extracted with 3×10 ml diethyl ether. The combined organic extracts were washed with brine, dried (Na_2SO_4), and concentrated *in vacuo*. Recrystallization from diethyl ether afforded **12** (250 mg, 72%) as colorless crystals.

Method B, starting from 3-bromoquinoline (**17**). 8.4 ml *n*-butyllithium (1.5 *M*; 12.5 mmol) were cooled to −78°C, and a solution of 1.4 ml **17** (10 mmol) in dry diethyl ether was added over 2 min. After 15 min, a solution of 1.05 g **18** (10 mmol) in 10 ml dry diethyl ether was added. The reaction mixture was allowed to warm to room temperature over 3 h and was then quenched with saturated aqueous ammonium chloride and extracted with 3×10 ml diethyl ether. The combined organic extracts were washed with brine, dried (Na_2SO_4), and evaporated *in vacuo*. Recrystallization from diethyl ether yielded **12** (820 mg, 48%) as colorless crystals.

M. p.: 132–134°C; ^{1}H NMR (80 MHz): $\delta = 9.42$ (1H, d, $J = 2.0$ Hz, 2-H), 8.70 (1H, d, $J = 2.0$ Hz, 4-H), 8.20–7.50 (4H, m, arom. H), 2.74 (3H, s, $COCH_3$) ppm; ^{13}C NMR (20.12 MHz): $\delta = 196.6$ (C = O), 149.7 (8a-C), 149.1 (2-C), 137.2 (4-C), 131.9, 129.4, 129.3 (5-C, 7-C and 8-C), 129.1 (4a-C), 127.5 (6-C), 126.7 (3-C), 26.7 ($CO\mathit{C}H_3$) ppm; IR (KBr): $\nu = 1680\,cm^{-1}$; MS: $m/z = 171$ (M^+).

3-(1-Methylprop-1-enyl)-quinoline (**13**; $C_{13}H_{13}N$)

Method A, starting from **12**. To a suspension of 410 mg carefully dried and pulverized ethyl-triphenyl-phosphonium bromide (1.1 mmol) in dry diethyl ether, 0.7 ml *n*-butyllithium (1.6 *M*; 1.1 mmol) were added under argon at 0°C. Dissolution of the salt and formation of the red ylide occurred within 15 min. Then, a solution of 170 mg **12** (1 mmol) in 8 ml dry diethyl ether was added dropwise by means of a syringe at room temperature, and the reaction mixture was stirred under reflux for 6 h. After cooling to room temperature it was filtrated to remove triphenylphosphane oxide. The resulting filtrate was washed with water and brine, dried (Na_2SO_4), and concentrated *in vacuo*. The product was purified by column chromatography (diethyl ether: light petroleum = 1:3) affording *Z*-**13** (70 mg; 38%) and *E*-**13** (60 mg, 33%) as colorless oils.

Method B, starting from 1-methyl-1-(quinolin-3-yl)-propanol (**14**). 400 mg **14** (2 mmol) were dissolved in 20 ml 6 *N* HCl and heated under reflux for 4 h. Under cooling with ice the solution was carefully alkalized with NaOH and extracted with 3×10 ml CH_2Cl_2. The combined organic layers were washed with brine, dried (Na_2SO_4), and evaporated under reduced pressure. The residue was purified by flash chromatography (diethyl ether) affording *E*-**13** (240 mg, 65%) as a yellowish oil.

E-**13**: ^{1}H NMR (80 MHz):$\delta = 9.02$ (1H, br, 2-H), 8.15–7.37 (5H, m, arom. H), 6.07 (1H, q, $J = 6.7$ Hz, 2′-H), 2.13 (3H, m, 1′-CH_3), 1.88 (3H, d, $J = 6.7$ Hz, 3′-H) ppm; ^{13}C NMR (20.12 MHz): $\delta = 149.3$ (2-C), 146.8 (8a-C), 136.2 (1′-C), 132.6 (3-C), 131.0, 129.0, 128.9, 127.9, 127.0 (arom. CH), 128.6 (4a-C), 124.9 (2′-C), 15.2, 14.4 (1′-CH_3, 3′-C) ppm; IR (KBr): $\nu = 3050$, $1500\,cm^{-1}$; MS: $m/z = 183$ (M^+).

Z-**13**: ^{1}H NMR (80 MHz): $\delta = 8.81$ (1H, br, 2-H), 8.20–7.40 (5H, m, arom. H), 5.78 (1H, q, $J = 6.7$ Hz, 2′-H), 2.12 (3H, m, 1′-CH_3), 1.65 (3H, dq, $J = 6.7$ Hz, 3′-H) ppm; ^{13}C NMR (20.12 MHz): $\delta = 151.1$ (2-C), 147.1 (8a-C), 134.9 (1′-C), 133.6 (3-C), 134.1, 129.3, 128.9, 127.7,

126.6 (arom. CH), 128.0 (4a-C), 124.1 (2′-C), 25.1, 14.9 (1′-CH_3, 3′-C) ppm; IR (KBr): $\nu = 2880$, 1490 cm^{-1}; MS: $m/z = 183$ (M^+).

1-Methyl-1-(quinolin-3-yl)-propanol (**14**; $C_{13}H_{15}NO$) *and 3-acetyl-3-ethyl-1,2-dihydroquinoline* (**15**; $C_{13}H_{15}NO$)

A solution of 690 mg **12** (4 mmol) in 10 ml diethyl ether was cooled to 0°C. After addition of 1.7 ml ethylmagnesium bromide (1.8 *M*; 3 mmol), the solution was allowed to warm to room temperature over 2 h. Then, the reaction mixture was quenched with saturated aqueous NH_4Cl and extracted with 3×10 ml diethyl ether. The combined organic layers were washed with brine, dried (Na_2SO_4), and evaporated *in vacuo*. The resulting green-yellow oil represented a mixture of alcohol **14** and ketone **15** which could be separated by dissolution in 20 ml CH_2Cl_2 and extraction with 3 × 10 ml aqueous citric acid (10%). Work-up of the organic layer afforded after drying (Na_2SO_4) and evaporation of the solvent *in vacuo* **15** (230 mg, 28%) as a yellow oil.

^{1}H NMR (80 MHz): $\delta = 7.49$ (1H, d, $J = 5.3$ Hz, 4-H), 7.28–6.65 (5H, m, arom. H, NH), 4.12 (1H, t, $J = 5.3$ Hz, 2-H), 2.29 (3H, s, $COCH_3$), 1.75–1.15 (2H, m, CH_2CH_3), 0.73 (3H, t, $J = 7.5$ Hz, CH_2CH_3) ppm; ^{13}C NMR (20.12 MHz):$\delta = 194.8$ (C = O), 139.7 (4-C), 136.6 (8a-C), 129.5, 126.6, 123.4, 114.5 (arom. CH), 125.4 (3-C), 113.2 (4a-C), 35.9 (2-C), 30.7 (CH_2CH_3), 24.4 ($COCH_3$) 9.4 (CH_2CH_3) ppm; IR (KBr): $\nu = 1650$, 1600 cm^{-1}; MS: $m/z = 201$ (M^+).

Alkalization of the combined aqueous layers with NaOH and subsequent extraction with 3×10 ml CH_2Cl_2 yielded after drying (Na_2SO_4) and evaporation of the solvent under reduced pressure **14** (280 mg, 35%) as a yellow oil.

^{1}H NMR (80 MHz): $\delta = 8.85$ (1H, d, $J = 2.1$ Hz, 2-H), 8.22 (1H, d, $J = 2.1$ Hz, 4-H), 8.07–7.30 (4H, m, arom. H), 4.18 (1H, br, OH), 1.88 (2H, q, $J = 8.0$ Hz, CH_2CH_3), 1.60 (3H, s, 1′-CH_3), 0.78 (3H, t, $J = 8.0$ Hz, CH_2CH_3) ppm; ^{13}C NMR (20.12 MHz): $\delta = 148.8$ (2-C), 146.6 (8a-C), 140.5 (3-C), 131.7 (4-C), 127.6 (4a-C), 129.0, 128.6, 127.8, 126.5 (arom. CH), 73.6 (1′-C), 36.5 (CH_2CH_3), 29.4 (1′-CH_3), 8.2 (CH_2CH_3) ppm; IR (KBr): $\nu = 3100$, 2500 cm^{-1}; MS: $m/z = 201$ (M^+).

Formation of 2-methyl-3-(1-methylprop-1-enyl)-1,2-dihydroquinoline (**16**; $C_{14}H_{17}N$) *and subsequent N-acylation to derivatives* **3** *(general procedure)*

A flame-dried flask, containing 10 ml CH_3Li (1.4 *M*; 14 mmol) was cooled to 0°C. After addition of 2.1 g **13** (11 mmol), the mixture was stirred at room temperature for 2 h, quenched with saturated aqueous NH_4Cl, and extracted with 3×20 ml diethyl ether. The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated *in vacuo*. The residue was used without further purification. The 2-methyl-1,2-quinoline derivative (10 mmol) was dissolved in 20 ml CH_2Cl_2 and cooled to 0°C. After addition of 1.5 ml triethylamine (11 mmol), the solution was treated with the selected chloroformate (10.5 mmol) and stirred for 2–6 h (TLC control). Water was added, and the aqueous layer was extracted with 3×20 ml CH_2Cl_2. The combined extracts were washed with 1 *N* HCl, 2 *N* Na_2CO_3, and brine, dried (Na_2SO_4), and concentrated under reduced pressure. Reductive alkylation of 420 mg **13** (2 mmol) with CH_3Li and subsequent acylation with ethyl chloroformate yielded **3** (R^1 = Et, R^2 = Me; $C_{17}H_{21}NO_2$; 350 mg, 65%) as a yellow oil.

^{1}H NMR (80 MHz): $\delta = 7.74$–6.50 (5H, m, arom. H, 4-H), 5.92 (1H, q, $J = 6.8$ Hz, 2′-H), 5.75 (1H, q, $J = 6.6$ Hz, 2-H), 4.21 (2H, q, $J = 7.2$ Hz, OCH_2CH_3), 1.90 (3H, s, 1′-CH_3), 1.80 (3H, d, $J = 6.8$ Hz, 3′-H), 1.30 (3H, t, $J = 7.2$ Hz, OCH_2CH_3), 1.15 (3H, d, $J = 6.5$ Hz, 2-CH_3) ppm; ^{13}C NMR (20.12 MHz): $\delta = 155.5$ (C = O), 144.2 (1′-C), 134.7 (8a C), 134.4 (4-C), 131.9 (3-C), 128.2 (4a-C), 129.2, 128.6, 127.8, 126.5 (arom. CH), 117.8 (2′-C), 61.1 (OCH_2CH_3), 48.6 (2-C), 17.3 (2-CH_3), 14.7 (OCH_2CH_3), 14.3 (1′-CH_3), 13.7 (3′-C) ppm; IR (KBr): $\nu = 1715$ cm^{-1}; MS: $m/z = 271$ (M^+).

References

[1] Drautz H, Zähner H, Kupfer E, Keller-Schierlein W (1981) Helv Chim Acta **64**: 1752
[2] Karrer A, Dobler M (1982) Helv Chim Acta **65**: 1432
[3] Wiesner M, Thiem J (1989) J Carbohydr Chem **8**: 705
[4] Kratzel M, Weigl A (1997) J Chem Soc Perkin Trans 1, 1009
[5] Nahm S, Weinreb SM (1981) Tetrahedron Lett **22**: 3815
[6] Hecht H (1985) Diploma thesis, University of Vienna
[7] Roberts R (1983) J Org Chem **48**: 2053

Received January 7, 1998. Accepted (revised) March 16, 1998