1-ACYL-2-ALKYL-3,4-EPOXY-1,2,3,4-TETRAHYDRO-QUINOLINES - SYNTHESIS AND REACTIONS WITH *N*-NUCLEOPHILES

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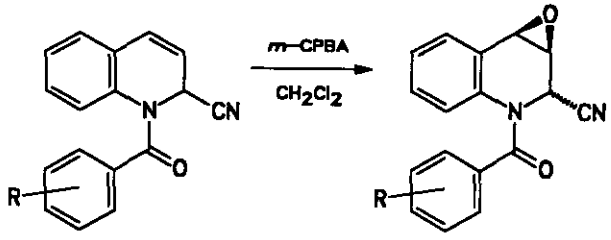
Abstract - Epoxide opening of the title compounds (6) with primary or secondary amines using lithium perchlorate as catalyst gave 1,2,3,4-tetrahydroquinolines with stereochemically well defined substitution pattern in the piperidine moiety (7, 8). By-products (9, 10), formed by acyl migration, were observed.

We recently reported that quinoline Reissert compounds (1) can be converted to 3,4-epoxides (2) by reaction with peracids (Scheme 1).[1,2]



1 2

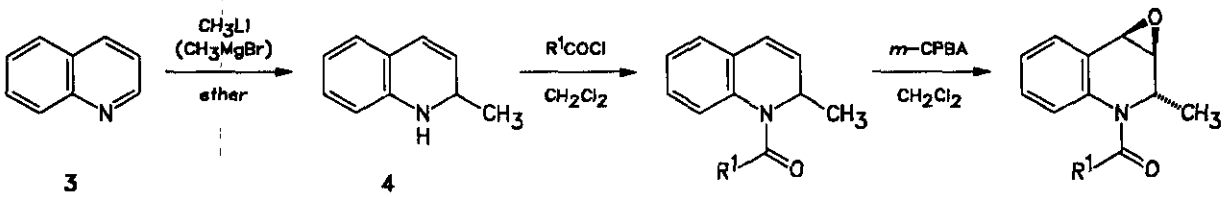
Only relative stereochemistry shown throughout.

Scheme 1

Although these compounds combine a 1,2-dihydroquinoline partial structure with an oxirane moiety, they show a surprising stability in crystalline state. On the other hand, in solution they readily react with *N*-nucleophiles like primary or secondary amines.[3] Our efforts to get an approach to

4-*N*-substituted quinoline derivatives by nucleophilic oxirane ring opening were not successful, because the starting epoxides undergo fragmentation to benzamides and 4-hydroxyquinoline. This reaction is caused by elimination of the 2-CN substituent.[3] We therefore studied the ring opening behaviour on derivatives with a not-removable substituent instead of the nitrile moiety. For this purpose we synthesized 2-alkyl derivatives[2] whose reactivity was investigated on the 2-methyl congeners (**6**) offering an approach to substituted 1,2,3,4-tetrahydroquinolines of pharmaceutical interest.

Outgoing from quinoline (**3**) the 2-alkyl-1,2-dihydro derivatives (**4**) were prepared according to a literature procedure[4] and then acylated by acid halides. Subsequently, the intermediates (**5**) were oxidized to the corresponding epoxides (**6**) by *m*-chloroperoxybenzoic acid in good to excellent yields (Scheme 2). Various acyl groups were introduced to get information if there might be an influence on the oxirane ring cleavage, since the mechanism of the ring opening of 2,2-dimethyl analogues of **6e** is described as initial attack of the nucleophile on the *N*-acetyl group, which is removed, followed by the entry of the nucleophile at position 4 of the planar intermediate, yielding the *cis*- and *trans*-products.[5]



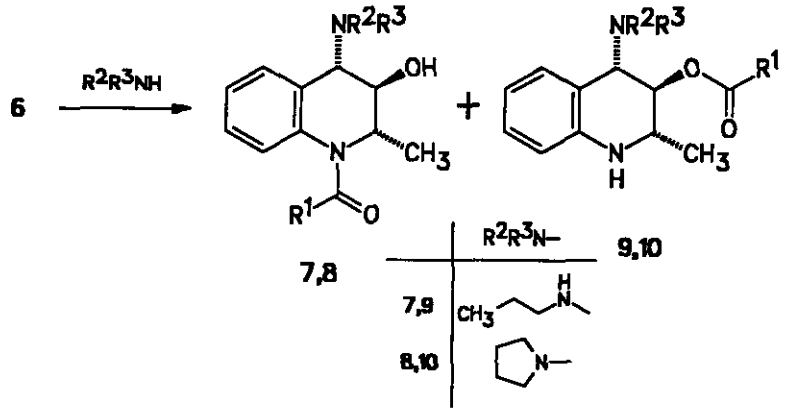
3 **4** **5** **6**

Scheme 2

	R^1		R^1
a	Ph-	d	4-NO_2-Ph-
b	4-CH_3-Ph-	e	CH_3-
c	3,4,5-$(OCH_3)_3$-Ph-	f	$(CH_3)_3$-C-

As observed on the Reissert analogues (**2**) the epoxidation afforded only one diastereomer. The relative stereochemistry of **6** was confirmed by an X-ray analysis (of **6b**) which revealed the *trans* stereochemistry of oxirane ring and 2-methyl group.[2] The ^1H nmr measurements demonstrate that the relative configuration of **6** complies with the assumed relative configuration of the Reissert epoxides (**2**).

The oxirane ring opening was exemplified by reaction of **6** with *n*-propylamine or pyrrolidine as *N*-nucleophiles (Scheme 3).

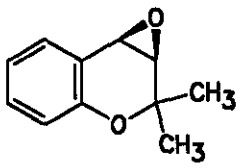


Scheme 3

		Product ratio (reaction time: 3 h)		
Starting compound	Amine	*N*-acyl product	*O*-acyl product	recovered educt
6b	*n*-propylamine	38 % **7b**	1 % **9b**	57 % **6b**
	pyrrolidine	62 % **8b**	6 % **10b**	28 % **6b**
6c	*n*-propylamine	31 % **7c**	3 % **9c**	59 % **6c**
	pyrrolidine	47 % **8c**	6 % **10c**	33 % **6c**
6d	*n*-propylamine	35 % **7d**	3 % **9d**	58 % **6d**
	pyrrolidine	45 % **8d**	16 % **10d**	21 % **6d**
6e	*n*-propylamine	32 % **7e**	2 % **9e**	57 % **6e**
	pyrrolidine	65 % **8e**	5 % **10e**	24 % **6e**

Ring opening experiments by heating the epoxide with an excess of amine in a protic solvent afforded only small amounts of β-amino alcohols (**7**) or (**8**), respectively. These results are in accordance with aminolyses on disubstituted epoxides which generally require forcing conditions[6] and are also reported from precursors of cromakalim bearing a comparable epoxide moiety.[7] On the other hand, using of metal ions as catalysts can significantly enhance the efficiency of oxirane ring opening.[8] A powerful catalyst is ceric ammonium nitrate which obviously cannot be allowed by its oxidizing properties.[9] In the present case, we used lithium perchlorate according to Crotti et *al.*[10] Following this procedure we achieved good results in oxirane ring opening. Fortunately, the epoxide ring was attacked selectively at the benzylic position, affording the diastereomerically pure amino alcohols (**7**)

or (**8**), respectively, which still carry the *N*-acyl group. The postulated structure was confirmed by a ^{1}H-^{13}C-heteronuclear correlation spectrum of **8b**. The observed regioselectivity is in agreement with oxirane ring openings on comparable structures (**11** - **13**), in all examples the nucleophile enters the 4-position.[5,7,11]



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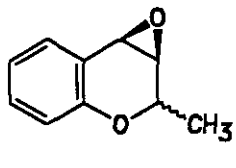

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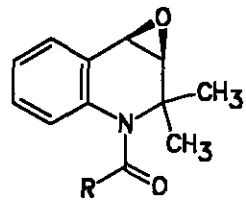

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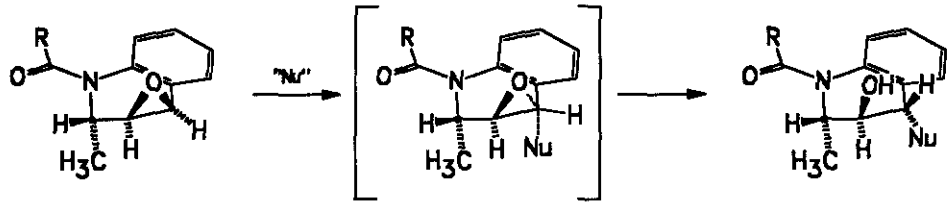
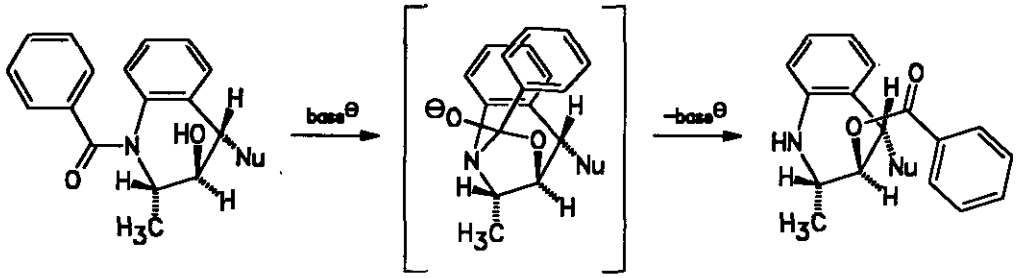
In our case, the amide forces a nearly planare and inflexible tetrahydropyridine ring, therefore, the nucleophile can only approach from the rear (see transition state **14**). From the synthetic path it is evident, that the new substituent at C-4 and the resulting OH-group at C-3 must be orientated *trans*. In this way we are able to synthesize 1,2,3,4-tetrasubstituted tetrahydroquinolines with well defined relative stereochemistry.



6 **14** **7,8**

Since the acyl group is not participating in the epoxide cleavage, a significant influence of the acyl group on the oxirane ring opening could no longer be expected. This was also seen if the ring opening reaction was performed under restricted conditions: the epoxide was dissolved in acetonitrile and heated with 1 equivalent of amine and metal salt for 3 h under reflux. After workup the mixture was separated by column chromatography which revealed comparable ratios of product and starting material for all tested compounds (**6b-e**). Under the given conditions we were able to isolate a small amount of a by-product, which is characterized in the ^{1}H nmr spectrum by a down-field shift of 3-H, the 2-H shows the opposite effect while the couplings remain unaffected. These data are in accordance with the structures of compounds (**9**) and (**10**), respectively, whose generation can be

explained by migration of the acyl moiety *via* a five-membered intermediate (**15**) which is allowed by the *trans* position of the substituents on carbons 2 and 3.



7,8 **15** **9,10**

The formation of derivatives (**7**) and (**8**) could be promoted using a longer reaction time, while the addition of more than one equivalent of amine to the reaction mixture forced the conversion to **9** and **10**, respectively.

EXPERIMENTAL SECTION

Melting points were taken on a Kofler hot stage apparatus and are uncorrected. Solvents and common reagents were obtained commercially and used as received or purified as follows: dichloromethane was distilled under nitrogen from phosphorus pentoxide, tetrahydrofuran was refluxed under argon over sodium benzophenone ketyl and distilled. Elemental analyses were performed by Mag. J. Theiner, Institut für Physikalische Chemie der Universität Wien. Ir spectra were recorded as KBr pellets in the case of solids or as liquid films between KBr salt disks in the case of oils, using a Perkin Elmer model 298 spectrophotometer. Nmr spectra were determined on a Bruker AC 80 (the ^{13}C spectrum of **6a** was recorded on a Varian Unity-plus 300). All substances were measured in $CDCl_3$ as solvent. ^1H nmr spectra were recorded with $(CH_3)_4Si$ as the internal reference, the chemical shifts of the ^{13}C spectra were given in ppm related to the resonance of $CDCl_3$ (77.0 ppm), an asterisk marks peaks of double intensity. Mass spectra were recorded on a Hewlett-Packard GC-MS equipment (HP-5890A, HP-5970C, HP-59970). Column chromatography was conducted on Merck silica gel 60.

General Procedure for *N*-Acylation of Dihydroquinolines (4)

To a stirred solution of 2-methyl-1,2-dihydroquinoline (**4**) (1.38 g, 9.5 mmol) in dichloromethane (20 ml), triethylamine (1.39 ml, 10 mmol) was added, followed by a solution of the selected acyl chloride (9.0 mmol) in dichloromethane (10 ml) under ice cooling. Then, the reaction mixture was

stirred at room temperature overnight. Finally, the organic layer was washed with hydrochloric acid (2N, 2 x 10 ml), saturated sodium bicarbonate solution (2 x 10 ml) and brine (2 x 10 ml). The organic layer was separated, dried (Na_2SO_4) and evaporated *in vacuo.*

1-Benzoyl-2-methyl-1,2-dihydroquinoline (5a): Prepared by acylation with benzoyl chloride (1.04 ml, 9.0 mmol): 2.00 g of **5a** (89 %) as off-white crystals. mp 128 - 130 °C (*ether*); ^{1}H-nmr: δ (ppm) 7.70 - 6.70 (9H, m, arom. H), 6.53 (1H, br d, J = 9 Hz, 4-H), 6.12 (1H, dd, J = 6 Hz, J = 9 Hz, 3-H), 5.28 (1H, m, 2-H), 1.20 (3H, d, J = 7 Hz, 2-CH_3); ^{13}C-nmr: δ (ppm) 169.3 (C=O), 135.8 (8a-C), 134.9 (1'-C), 126.9 (4a-C), 131.6, 130.0, 128.7*, 127.8*, 126.4, 125.9, 125.6, 124.5, 123.8 (arom. C-H, 3-C, 4-C), 48.6 (2-C), 17.4 (2-CH_3); ir: 1640 cm^{-1} (ν_{amide}); ms (m/z) 249 (M^+). Anal. Calcd for $C_{17}H_{15}NO$: C, 81.90; H, 6.06; N, 5.62. Found: C, 81.82; H, 6.02; N, 5.52.

2-Methyl-1-(*p*-toluoyl)-1,2-dihydroquinoline (5b): See ref. 2.

2-Methyl-1-(3,4,5-trimethoxybenzoyl)-1,2-dihydroquinoline (5c) : Prepared by acylation with 3,4,5-trimethoxybenzoyl chloride (2.08 g, 9.0 mmol), additional purification by column chromatography (petroleum ether/ether: 1:1): 2.35 g of **5c** (72 %) as off-white crystals. mp 171 - 172 °C (ether); ^{1}H-nmr: δ (ppm) 7.16 - 6.77, 6.60 - 6.49 (7H, m, arom. H, 4-H), 6.15 (1H, dd, J = 5 Hz, J = 10 Hz, 3-H), 5.29 (1H, m, 2-H), 3.83 (3H, s, 4'-OCH_3), 3.65 (6H, s, 3'- and 5'-OCH_3), 1.20 (3H, d, J = 7 Hz, 2-CH_3); ^{13}C-nmr: δ (ppm) 168.9 (C=O), 152.5* (3'-C, 5'-C), 139.7, 135.1, 130.2, 126.8 (4a-C, 8a-C, 1'-C, 4'-C), 131.8, 126.6, 125.8, 125.6, 124.6, 123.7 (3-C, 4-C, 5-C, 6-C, 7-C, 8-C), 106.7* (2'-C, 6'-C), 60.6 (4'-OCH_3), 55.8* (3'-OCH_3, 5'-OCH_3), 48.8 (2-C), 17.4 (2-CH_3); ir: 1650 cm^{-1} (ν_{amide}); ms (m/z) 339 (M^+). Anal. Calcd for $C_{20}H_{21}NO_4$: C, 70.78; H, 6.24; N, 4.13. Found: C, 70.53; H, 6.19; N, 4.01.

2-Methyl-1-(*p*-nitrobenzoyl)-1,2-dihydroquinoline (5d) : Prepared by acylation with 4-nitrobenzoyl chloride (1.67 g, 9.0 mmol): 2.10 g of **5d** (79 %) as yellow crystals. mp 174 - 176 °C (dichloromethane/ether); ^{1}H-nmr: δ (ppm) 8.12 (2H, d, J = 9 Hz, 3'-H, 5'-H), 7.48 (2H, d, J = 9 Hz, 2'-H, 6'-H), 7.27 - 6.38 (5H, m, arom. H, 4-H), 6.19 (1H, dd, J = 5.5 Hz, J = 9.5 Hz, 3-H), 5.33 (1H, m, 2-H), 1.22 (3H, d, J = 7 Hz, 2-CH_3); ^{13}C-nmr: δ (ppm) 167.2 (C=O), 148.4 (4'-C), 141.9 (1'-C), 134.0 (8a-C), 131.9, 129.9*, 126.9, 126.5, 125.6*, 123.9, 123.3 (arom. C-H, 3-C, and 4-C), 127.4 (4a-C), 48.9 (2-C), 17.4 (2-CH_3); ir: 1650 (ν_{amide}), 1525, 1340 cm^{-1} (νNO_2); ms (m/z) 294 (M^+). Anal. Calcd for $C_{17}H_{14}N_2O_3$: C, 69.38; H, 4.79; N, 9.52. Found: C, 69.62; H, 4.74; N, 9.48.

1-Acetyl-2-methyl-1,2-dihydroquinoline (5e) : Prepared by acylation with acetyl chloride (0.65 ml, 9.0 mmol): 1.45 g of **5e** (86 %) as yellow oil. ^{1}H-Nmr: δ (ppm) 7.16 (4H, br s, arom. H), 6.47 (1H, d, J = 9 Hz, 4-H), 6.10 (1H, dd, J = 6 Hz, J = 9 Hz, 3-H), 5.42 (1H, m, 2-H), 2.22 (3H, s, CO-CH_3),

1.03 (3H, d, J = 7 Hz, 2-CH_3); ^{13}C-nmr: δ (ppm) 169.7 (C=O), 134.7 (8a-C), 132,8, 127.0, 126.3, 125.3, 124.8, 123.9 (arom. C-H, 3-C and 4-C), 128.2 (4a-C), 47.1 (2-C), 22.8 (CO-CH_3), 17.5 (2-CH_3); ir: 1660 cm^{-1} (ν_{amide}); ms (m/z) 187 (M^+). Anal. Calcd for $C_{12}H_{13}NO$: C, 76.98; H, 7.00; N, 7.48. Found: C, 76.77; H, 7.02; N, 7.73.

2-Methyl-1-pivaloyl-1,2-dihydroquinoline (5f) : Prepared by acylation with pivaloyl chloride (1.09 ml, 9.0 mmol): 1.09 g of **5f** (53 %) as yellow oil after additional purification by column chromatography (petroleum ether/ether: 1:1). ^{1}H-Nmr: δ (ppm) 7.50 - 6.95 (4H, m, arom. H), 6.48 (1H, d, J = 9 Hz, 4-H), 6.11 (1H, dd, J = 6 Hz, J = 9 Hz, 3-H), 4.95 (1H, m, 2-H), 1.25 (9H, s, C-(CH_3)$_3$); ^{13}C-nmr: δ (ppm) 177.9 (C=O), 134.8 (8a-C), 131.1, 126.3, 125.4, 124.5 (arom. C-H, 3-C and 4-C), 127.7 (4a-C), 49.0 (2-C), 39.9 (CO-C-(CH_3)$_3$), 28.8 (CO-C-(CH_3)$_3$), 17.1 (2-CH_3); ir: 1650 cm^{-1} (ν_{amide}); ms (m/z) 229 (M^+). Anal. Calcd for $C_{15}H_{19}NO$: C, 78.56; H, 8.35; N, 6.11. Found: C, 78.32; H, 8.46; N, 6.25.

General Procedure for Epoxidation of 1-Acyl-2-alkyl-dihydroquinolines (5)

To an ice-cooled solution of **5a-f** (5 mmol) in dichloromethane (50 ml), *m*-chloroperoxybenzoic acid (2.60 g, 50%, 7.5 mmol) was added with stirring. After 15 min the ice bath was removed, and the mixture was stirred for 2 h at room temperature. The disappearance of the starting material was controlled by tlc. Sodium carbonate solution (2N, 25 ml) was added, and the solution was stirred for further 10 min. The aqueous phase was extracted with dichloromethane (3 x 40 ml), the combined organic layers were washed with sodium carbonate solution (2N, 2 x 20 ml), dried (Na_2SO_4) and evaporated.

1-Benzoyl-3,4-epoxy-2-methyl-1,2,3,4-tetrahydroquinoline (6a) : Prepared from 1.24 g of **5a**: colorless crystals from dichloromethane/ether, mp 182-184 °C; additional purification of the mother liquor by column chromatography (petroleum ether/ether: 1:1), total yield 900 mg (68 %); ^{1}H-nmr: δ (ppm) 7.50 - 7.12, 7.10 - 6.82 (8H, each m, arom. H), 6.58 - 6.38 (1H, m, arom. H), 5.34 (1H, dq, J = 2.2 Hz, J = 6.7 Hz, 2-H), 3.98 (1H, d, J = 4.3 Hz, 4-H), 3.80 (1H, dd, J = 2.2 Hz, J = 4.3 Hz, 3-H), 1.14 (3H, d, J = 6.7 Hz, 2-CH_3); ^{13}C-nmr: δ (ppm) 171.1 (C=O), 136.1, 136.0, 130.2, 129.3, 129.0*, 128.4, 128.0*, 127.2, 125.6, 124.9 (arom. C), 62.1 (4-C), 50.8 (3-C), 45.5 (2-C), 14.2 (2-CH_3); ir: 1650 cm^{-1} (ν_{amide}); ms (m/z) 265 (M^+). Anal. Calcd for $C_{17}H_{15}NO_2$: C, 76.96; H, 5.69; N, 5.27. Found: C, 76.67; H, 5.71; N, 5.16.

3,4-Epoxy-2-methyl-1-(*p*-toluoyl)-1,2,3,4-tetrahydroquinoline (6b): See ref. 2.

3,4-Epoxy-2-methyl-1-(3,4,5-trimethoxybenzoyl)-1,2,3,4-tetrahydroquinoline (6c): Prepared from 1.70 g of **5c**: colorless crystals from diethylether, mp 168 - 171 °C; additional purification of the mother liquor by column chromatography (ether), total yield 1.51 g (85 %); ^{1}H-nmr: δ (ppm) 7.55 - 7.30 (1H, m, arom. H), 7.17 - 6.95 (2H, m, arom. H), 6.70 - 6.41 (3H, m, arom. H), 5.32 (1H, m, 2-H), 3.98 (1H, d, J = 3.9 Hz, 4-H), 3.82 (1H, m, 3-H), 3.80 (3H, s, 4'-OCH_3), 3.64 (6H, s, 3'-OCH_3, 5'-OCH_3), 1.14 (3H, d, J = 6.8 Hz, 2-CH_3); ^{13}C-nmr: δ (ppm) 170.1 (C=O), 152.4*, 139.5, 136.1, 130.4, 129.0, 128.4, 126.8, 125.1, 124.7, 106.6* (arom. C), 61.9 (4-C), 60.6 (4'-OCH_3), 55.7* (3'-OCH_3, 5'-OCH_3), 50.6 (3-C), 45.4 (2-C), 14.0 (2-CH_3); ir: 1650 cm^{-1} (ν_{amide}); ms (m/z) 355 (M^+). Anal. Calcd for $C_{20}H_{21}NO_5$: C, 67.59; H, 5.95; N, 3.94. Found: C, 67.30; H, 6.02; N, 3.94.

3,4-Epoxy-2-methyl-1-(*p*-nitrobenzoyl)-1,2,3,4-tetrahydroquinoline (6d): Prepared from 1.47 g of **5d**: yellowish crystals from ether, mp 153 - 155 °C; additional purification of the mother liquor by column chromatography (petroleum ether/ether: 1:2), total yield 1.44 g (93 %); ^{1}H-nmr: δ (ppm) 8.08 (2H, d, J = 9.0 Hz, 3'-H, 5'-H), 7.54 (2H, d, J = 9.0 Hz, 2'-H, 6'-H), 7.60 - 7.40 (1H, m, arom. H), 7.03 (2H, m, arom. H), 6.40 (1H, m, arom. H), 5.38 (1H, dq, J = 2.3 Hz, J = 6.9 Hz, 2-H), 4.01 (1H, d, J = 4.0 Hz, 4-H), 3.84 (1H, dd, J = 2.3 Hz, J = 4.0 Hz, 3-H), 1.14 (3H, d, J = 6.9 Hz, 2-CH_3); ^{13}C-nmr: δ (ppm) 168.1 (C=O), 148.4, 142.1, 135.0, 129.8*, 129.7, 128.8, 127.1, 126.0, 125.9, 123.2 (arom. C), 125.0 (4a-C), 61.6 (4-C), 50.7 (3-C), 45.6 (2-C), 14.0 (2-CH_3); ir: 1650 (ν_{amide}), 1530, 1340 cm^{-1} (ν_{NO_2}); ms (m/z) 310 (M^+). Anal. Calcd for $C_{17}H_{14}N_2O_4$: C, 65.80; H, 4.54; N, 9.02. Found: C, 65.86; H, 4.60; N, 8.87.

1-Acetyl-3,4-epoxy-2-methyl-1,2,3,4-tetrahydroquinoline (6e): Prepared from 940 mg of **5e**: colorless crystals from ether, mp 123 - 125 °C; additional purification of the mother liquor by column chromatography (ether), total yield 790 mg (78 %); ^{1}H-nmr: δ (ppm) 7.68 - 6.86 (4H, m, arom. H), 5.50 - 5.15 (1H, m, 2-H), 3.88 (1H, d, J = 3.9 Hz, 4-H), 3.70 (1H, dd, J = 2.4 Hz, J = 3.9 Hz, 3-H), 2.12 (3H, s, CO-CH_3), 0.95 (3H, d, J = 6.8 Hz, 2-CH_3); ^{13}C-nmr: δ (ppm) 170.6 (C=O), 135.5, 129.2, 128.5, 126.9, 126.4, 125.6 (arom. C), 61.0 (4-C), 50.0 (3-C), 43.2 (2-C), 22.5 (CO-$\underline{C}H_3$), 13.7 (2-CH_3); ir: 1660 cm^{-1} (ν_{amide}); ms (m/z) 203 (M^+). Anal. Calcd for $C_{12}H_{13}NO_2$: C, 70.91; H, 6.44; N, 6.89. Found: C, 70.63; H, 6.27; N, 6.74.

3,4-Epoxy-2-methyl-1-pivaloyl-1,2,3,4-tetrahydroquinoline (6f): Prepared from 1.14 g **5f**: spontaneously crystallizing oil, mp 63 - 68 °C, yield 540 mg (44 %); ^{1}H-nmr: δ (ppm) 7.50 - 7.05 (4H, m, arom. H), 5.05 (1H, dq, J = 2.4 Hz, J = 7.0 Hz, 2-H), 3.86 (1H, d, J = 4.2 Hz, 4-H), 3.70 (1H, dd, J = 2.4 Hz, J = 4.2 Hz, 3-H), 1.24 (9H, s, C-(CH_3)$_3$), 0.99 (3H, d, J =7.0 Hz, 2-CH_3); ^{13}C-nmr: δ (ppm) 179.3 (C=O), 136.1, 128.8, 128.0, 127.8, 126.5, 125.4 (arom. C), 61.1 (4-C), 50.1 (3-C), 46.7

(2-C), 40.6 (CO-C-$(CH_3)_3$), 29.0 (CO-C-$(CH_3)_3$), 14.0 (2-CH_3); ir: 1650 cm^{-1} (ν_{amide}); ms (m/z) 245 (M^+). Anal. Calcd for $C_{15}H_{19}NO_2$: C, 73.44; H, 7.80; N, 5.70. Found: C, 73.30; H, 8.06; N, 5.58.

General Procedure for Oxirane Ring Opening by *N*-Nucleophiles

A solution of the epoxide **6b-e** (1 mmol) in 2 ml of acetonitrile was treated with lithium perchlorate (110 mg, 1 mmol) and then stirred until complete solution of the salt occurred. After addition of the amine (1 mmol) the mixture was put into a hot oil bath to immediately start refluxation. After 3 h of reflux the oil bath was removed and the solution was allowed to cool for 10 min. The reaction mixture was diluted with water and extracted with dichloromethane (3 x 20 ml). The combined organic fractions were washed with water (2 x 10 ml), dried (Na_2SO_4) and evaporated *in vacuo*. The resulting product mixture was separated by column chromatography (ether).

3-Hydroxy-2-methyl-4-*n*-propylamino-1-*p*-toluoyl-1,2,3,4-tetrahydroquinoline (7b): Colorless crystals, mp 153 - 155 °C (ether); ^{1}H-nmr: δ (ppm) 7.44 - 6.77 (7H, m, arom. H), 6.50 (1H, dd, J = 8.0 Hz, J = 1.5 Hz, arom. H), 4.60 (1H, dq, J = 6.5 Hz, J = 6.0 Hz, 2-H), 3.53 (1H, d, J = 10.0 Hz, 4-H), 3.23 - 2.45 (5H, m, 3-H, propyl-1-H), NH, and OH), 2.30 (3H, s, 4'-CH_3), 1.94 - 1.35 (2H, m, propyl-2-H), 1.30 (3H, d, J = 6.5 Hz, 2-CH_3), 1.03 (3H, t, J = 7.0 Hz, propyl-CH_3); ^{13}C-nmr: δ (ppm) 169.1 (C=O), 140.4, 137.6, 133.4, 132.5, 128.7*, 128.5*, 126.6, 126.5, 125.6, 123.8 (arom. C), 79.6 (3-C), 61.1 (4-C), 56.5 (2-C), 50.8 (propyl-1-C), 23.7 (propyl-2-C), 21.3 (4'-CH_3), 19.4 (2-CH_3), 11.8 (propyl-CH_3); ir: 1625 cm^{-1} (ν_{amide}); ms (m/z) 338 (M^+). Anal. Calcd for $C_{21}H_{26}N_2O_2$: C, 74.52; H, 7.74; N, 8.27. Found: C, 74.62; H, 7.72; N, 8.25.

3-Hydroxy-2-methyl-4-*n*-propylamino-1-(3,4-5-trimethoxybenzoyl)-1,2,3,4-tetrahydroquinoline (7c): Colorless crystals, mp 141 - 142 °C (ether); ^{1}H-nmr: δ (ppm) 7.43 - 6.33 (6H, m, arom. H), 4.57 (1H, m, 2-H), 3.80 (3H, s, 4'-OCH_3), 3.60 (6H, s, 3'- and 5'-OCH_3), 3.58 (1H. d, J = 9.5 Hz, 4-H), 3.40 - 2.50 (4H, m, 3-H, propyl-1-H, hetero-H), 1.95 - 1.40 (3H, m, propyl-2-H, hetero-H), 1.34 (3H, d, J = 6.5 Hz, 2-CH_3), 1.03 (3H, t, J = 7.5 Hz, propyl-CH_3); ^{13}C-nmr: δ (ppm) 168.4 (C=O), 152.3, 137.8, 133.2, 129.9, 126.8, 126.6, 125.8, 123.5, 119.8, 106.6*, 104.9 (arom. C), 79.6 (3-C), 61.1, 60.7 (3-C, 4'-OCH_3), 56.6 (2-C), 55.7* (3'- and 5'-OCH_3), 50.8 (propyl-1-C), 23.7 (propyl-2-C), 19.4 (2-CH_3), 11.7 (propyl-CH_3); ir: 1645 cm^{-1} (ν_{amide}); ms (m/z) 414 (M^+). Anal. Calcd for $C_{23}H_{30}N_2O_5$: C, 66.64; H, 7.29; N, 6.75. Found: C, 66.56; H, 7.37; N, 6.63.

3-Hydroxy-2-methyl-1-*p*-nitrobenzoyl-4-*n*-propylamino-1,2,3,4-tetrahydroquinoline (7d): Yellow crystals, mp 186 - 187 °C (ether); ^{1}H-nmr: δ (ppm) 8.07, 7.38 (4H, AB-system, J = 9.0 Hz, arom. H),

7.30 - 6.80 (3H, m, arom. H), 6.45 (1H, d, J = 7.5 Hz, arom. H), 4.58 (1H, m, 2-H), 3.60 (1H, d, J = 10.0 Hz, 4-H), 3.30 - 2.25 (5H, m, 3-H, propyl-1-H, NH, and OH), 1.97 - 1.50 (2H, m, propyl-2-H), 1.37 (3H, d, J = 6.5 Hz, 2-CH_3), 1.06 (3H, t, J = 7.0 Hz, propyl-CH_3); ^{13}C-nmr: δ (ppm) 166.8 (C=O), 148.3, 141.7, 136.6, 133.9, 129.6*, 127.0, 126.6*, 123.8, 123.2* (arom. C), 79.2 (3-C), 60.8 (4-C), 56.5 (2-C), 50.9 (propyl-1-C), 23.9 (propyl-2-C), 19.3 (2-CH_3), 11.8 (propyl-CH_3); ir (KBr): 1650 (ν_{amide}), 1530, 1340 cm^{-1} (ν_{NO_2}); ms (m/z) = 369 (M^+). Anal. Calcd for $C_{20}H_{23}N_3O_4$: C, 65.02; H, 6.27; N, 11.37. Found: C, 65.06; H, 6.29; N, 11.26.

1-Acetyl-3-hydroxy-2-methyl-4-*n*-propylamino-1,2,3,4-tetrahydroquinoline (7e): Colorless crystals, mp 116 - 117 °C (ether); ^{1}H-nmr: δ (ppm) 7.37 - 6.97 (4H, m, arom. H), 4.52 (1H, m, 2-H), 3.35 (1H, d, J = 10.0 Hz, 4-H), 3.25 - 2.50 (4H, m, 3-H, propyl-1-H, hetero-H), 2.15 (3H, s, CO-CH_3), 1.95 - 1.40 (3H, m, propyl-2-H, hetero-H), 1.23 (3H, d, J = 7.0 Hz, 2-CH_3), 1.01 (3H, t, J = 7.0 Hz, propyl-CH_3); ^{13}C-nmr: δ (ppm) 169.1 (C=O), 136.4, 134.8, 126.6, 126.3, 125.4, 123.8 (arom. C), 78.7 (3-C), 60.6 (4-C), 55.4 (2-C), 50.6 (propyl-1-C), 23.4 (propyl-2-C), 22.1 (CO-$\underline{C}H_3$), 19.2 (2-CH_3), 11.5 (propyl-CH_3); ir: 1645 cm^{-1} (ν_{amide}); ms (m/z) 262 (M^+). Anal. Calcd for $C_{15}H_{22}N_2O_2$: C, 68.67; H, 8.45; N, 10.67. Found: C, 68.53; H, 8.35; N, 10.61.

3-Hydroxy-2-methyl-4-pyrrolidyl-1-*p*-toluoyl-1,2,3,4-tetrahydroquinoline (8b): Colorless crystals, mp 156 - 159 °C (ether); ^{1}H-nmr: δ (ppm) 7.38 - 6.76 (7H, m, arom. H), 6.56 (1H, dd, J = 7.0 Hz, J = 1.5 Hz, arom. H), 4.61 (1H, dq, J = 7.0 Hz, J = 5.0 Hz, 2-H), 4.03 (1H, d, J = 10.0 Hz, 4-H), 3.52 (1H, dd, J = 10.0 Hz, J = 5.0 Hz, 3-H), 3.33 - 2.90 (5H, m, pyrrolidyl-2-H and -5-H, OH), 2.29 (3H, s, 4'-CH_3), 2.14 - 1.87 (4H, m, pyrrolidyl-3-H and -4-H), 1.36 (3H, d, J = 7.0 Hz, 2-CH_3); ^{13}C-nmr: δ (ppm) 169.2 (C=O), 140.2, 138.2, 132.7, 130.8, 128.8*, 128.4*, 127.1, 126.2, 125.1, 124.8 (arom. C), 77.1 (3-C), 61.3 (4-C), 56.5 (2-C), 47.9* (pyrrolidyl-2-C and -5-C), 24.8* (pyrrolidyl-3-C and -4-C), 21.3 (4'-CH_3), 19.4 (2-CH_3); ir: 1625 cm^{-1} (ν_{amide}); ms (m/z) 350 (M^+). Anal. Calcd for $C_{22}H_{26}N_2O_2$: C, 75.39; H, 7.47; N, 7.99. Found: C, 75.32; H, 7.37; N, 7.92.

3-Hydroxy-2-methyl-4-pyrrolidyl-1-(3,4,5-trimethoxybenzoyl)-1,2,3,4-tetrahydroquinoline (8c): Colorless crystals, mp 171 - 173 °C (ether); ^{1}H-nmr: δ (ppm) 7.40 - 6.40 (6H, m, arom. H), 4.60 (1H, dq, J = 6.5 Hz, J = 5.0 Hz, 2-H), 4.03 (1H, d, J = 9.0 Hz, 4-H), 3.80 (3H, s, 4'-OCH_3), 3.60 (6H, s, 3'- and 5'-OCH_3), 3.51 (1H, dd, J = 9.0 Hz, J = 5.0 Hz, 3-H), 3.28 - 3.00 (5H, m, pyrrolidyl-2-H and -5-H, hetero-H), 2.15 - 1.88 (4H, m, pyrrolidyl-3-H and -4-H), 1.38 (3H, d, J = 6.5 Hz, 2-CH_3); ^{13}C-nmr: δ (ppm) 168.6 (C=O), 152.4*, 138.4, 130.5, 130.2, 127.2, 126.6, 125.0*, 106.6* (arom. C), 77.1 (3-C), 61.5, 60.8 (4-C and 4'-OCH_3), 56.7 (2-C), 55.8* (3'- and 5'-OCH_3), 47.9* (pyrrolidyl-2-C

and -5-C), 24.9* (pyrrolidyl-3-C and -4-C), 19.4 (2-CH_3); ir: 1640 cm^{-1} (ν_{amide}); ms (m/z) 426 (M^+). Anal. Calcd for $C_{24}H_{30}N_2O_5$: C, 67.58; H, 7.08; N, 6.56. Found: C, 67.32; H, 7.10; N, 6.41.

3-Hydroxy-2-methyl-1-*p*-nitrobenzoyl-4-pyrrolidyl-1,2,3,4-tetrahydroquinoline (8d): Yellow crystals, mp 230 - 233 °C (ether); ^{1}H-nmr: δ (ppm) 8.06 (2H, d, *J* = 9.0 Hz, arom. H), 7.46 - 6.77 (5H, arom. H), 6.48 (1H, dd, *J* = 7.5 Hz, *J* = 1.0 Hz, arom. H), 4.63 (1H, dq, *J* = 7.0 Hz, *J* = 5.5 Hz, 2-H), 4.05 (1H, d, *J* = 9.5 Hz, 4-H), 3.52 (1H, dd, *J* = 9.5 Hz, *J* = 5.5 Hz, 3-H), 3.29 - 2.96 (4H, m, pyrrolidyl-2-H and -5-H), 3.70 - 2.70, 2.40 - 1.40 (each 1H, br, NH and OH), 2.16 - 1.89 (4H, m, pyrrolidyl-3-H and -4-H), 1.40 (3H, d, *J* = 7.0 Hz, 2-CH_3); ^{13}C-nmr: δ (ppm) 166.9 (C=O), 148.3, 141.8, 137.1, 130.9, 129.6*, 127.1, 126.6, 125.8, 125.5, 123.2* (arom. C), 76.6 (3-C), 61.4 (4-C), 56.7 (2-C), 47.8* (pyrrolidyl-2-C and -5-C), 25.0* (pyrrolidyl-3-C and -4-C), 19.3 (2-CH_3); ir (KBr) 1640 (ν_{amide}), 1530, 1340 cm^{-1} (ν_{NO_2}); ms (m/z) 381 (M^+). Anal. Calcd for $C_{21}H_{23}N_3O_4$: C, 66.12; H, 6.07; N, 11.01. Found: C, 65.87; H, 5.88; N, 10.82.

1-Acetyl-3-hydroxy-2-methyl-4-pyrrolidyl-1,2,3,4-tetrahydroquinoline (8e): Colorless crystals, mp 158 - 159 °C (ether); ^{1}H-nmr: δ (ppm) 7.35 - 7.10 (4H, m, arom. H), 4.56 (1H, dq, *J* = 6.5 Hz, *J* = 6.0 Hz, 2-H), 3.80 (1H, d, *J* = 10.0 Hz, 4-H), 3.35 (1H, dd, *J* = 10.0 Hz, *J* = 6.0 Hz, 3-H), 3.55 - 3.20 (1H, br, OH), 3.20 - 2.98 (4H, m, pyrrolidyl-2-H and -5-H), 2.12 (3H, s, CO-CH_3), 2.10 - 1.87 (4H, m, pyrrolidyl-3-H and -4-H), 1.25 (3H, d, *J* = 6.5 Hz, 2-CH_3); ^{13}C-nmr: δ (ppm) 169.1 (C=O), 136.9, 132.2, 126.3, 125.8, 125.4, 125.1 (arom. C), 76.6 (3-C), 60.6 (4-C), 55.4 (2-C), 47.5* (pyrrolidyl-2-C and -5-C), 24.5* (pyrrolidyl-3-C and -4-C), 22.2 (CO-$\underline{C}H_3$), 19.2 (2-CH_3); ir: 1660 cm^{-1} (ν_{amide}); ms (m/z) 274 (M^+). Anal. Calcd for $C_{16}H_{22}N_2O_2$: C, 70.04; H, 8.08; N, 10.21. Found: C, 70.13; H, 8.06; N, 10.18.

2-Methyl-4-*n*-propylamino-3-*p*-toluoyloxy-1,2,3,4-tetrahydroquinoline (9b): Colorless oil; ^{1}H-nmr: δ (ppm) 7.97 (2H, d, *J* = 8.5 Hz, arom. H), 7.57 - 6.45 (6H, m, arom. H), 5.34 (1H, t, *J* = 9.0 Hz, 3-H), 4.18 (1H, d, *J* = 9.0 Hz, 4-H), 3.90 - 3.40 (2H, m, 2-H, NH; after D_2O-exchange: 1H, dq, *J* = 9.0 Hz, *J* = 6.5 Hz, 2-H), 2.90 - 2.30 (2H, m, propyl-1-H), 2.45 (3H, s, 4'-CH_3), 1.61 - 1.19 (3H, m, propyl-2-H), 1.26 (3H, d, *J* = 6.5 Hz, 2-CH_3), 0.87 (3H, t, *J* = 7.0 Hz, propyl-CH_3); ^{13}C-nmr: δ (ppm) 166.1 (C=O), 144.4, 143.8, 129.7*, 129.1*, 128.3, 127.8, 127.2, 122.2, 118.0, 113.8 (arom. C), 74.0 (3-C), 59.3 (4-C), 51.2 (2-C), 46.1 (propyl-1-C), 23.9 (propyl-2-C), 21.6 (4'-CH_3), 18.9 (2-CH_3), 11.7 (propyl-CH_3); ir: 1715 cm^{-1} (ν_{ester}); ms (m/z) 338 (M^+).

2-Methyl-4-*n*-propylamino-3-(3,4,5-trimethoxybenzoyloxy)-1,2,3,4-tetrahydroquinoline (9c): Yellowish oil; ^{1}H-nmr: δ (ppm) 7.65 - 6.50 (6H, m, arom. H), 5.36 (1H, t, *J* = 9.0 Hz, 3-H), 4.18 (1H, d, *J* = 9.0 Hz, 4-H), 3.92 (3H, s, 4'-OCH_3), 3.91 (6H, s, 3'- and 5'-OCH_3), 3.63 (1H, dq,

J = 9.0 Hz, J = 6.5 Hz, 2-H), 2.90 - 2.20 (3H, m, propyl-1-H, NH; after D_2O-exchange: 2H, m), 1.64 - 1.15 (2H, m, propyl-2-H), 1.26 (3H, d, J = 6.5 Hz, 2-CH_3), 0.85 (3H, t, J = 7.0 Hz, propyl-CH_3); ir: 1720 cm^{-1} (ν_{ester}); ms (m/z) 414 (M^+).

2-Methyl-3-*p*-nitrobenzoyloxy-4-*n*-propylamino-1,2,3,4-tetrahydroquinoline (9d): Colorless oil; ^{1}H-nmr: δ (ppm) 8.27 (2H, s, arom. H), 8.45 - 7.95 (1H, m, arom. H), 7.59 - 6.46 (5H, m, arom. H), 5.37 (1H, t, J = 8.5 Hz, 3-H), 4.17 (1H, d, J = 8.5 Hz, 4-H), 4.00 - 3.25 (2H, m, 2-H, NH), 2.57 (2H, q, J = 7.0 Hz, propyl-1-H), 1.75 - 1.10 (3H, m, propyl-2-H and NH), 1.30 (3H, d, J = 6.5 Hz, 2-CH_3), 0.82 (3H, t, J = 7.0 Hz, propyl-CH_3); ir: 1730 (ν_{ester}), 1530, 1340 cm^{-1} (ν_{NO_2}); ms (m/z) 369 (M^+).

3-Acetoxy-2-methyl-4-*n*-propylamino-1,2,3,4-tetrahydroquinoline (9e): Colorless oil; ^{1}H-nmr: δ (ppm) 7.80 - 6.40 (5H, m, arom. H, hetero-H), 5.10 (1H, t, J = 8.5 Hz, 3-H), 3.98 (1H, d, J = 8.5 Hz, 4-H), 3.55 - 3.25 (2H, m, 2-H, hetero-H), 2.51 (2H, q, J = 7.0 Hz, propyl-1-H), 2.12 (3H, s, CO-CH_3), 1.80 - 1.30 (2H, m, propyl-2-H), 1.22 (3H, d, J = 6.5 Hz, 2-CH_3), 0.95 (3H, t, J = 7.0 Hz, propyl-CH_3); ir: 1740 cm^{-1} (ν_{ester}); ms (m/z) = 262 (M^+).

2-Methyl-4-pyrrolidyl-3-*p*-toluoyloxy-1,2,3,4-tetrahydroquinoline (10b): Colorless crystals, mp 148 - 150 °C (ether); ^{1}H-nmr: δ (ppm) 8.00 (2H, d, J = 8.0 Hz, arom. H), 7.53 - 6.48 (6H, m, arom. H), 5.59 (1H, t, J = 7.5 Hz, 3-H), 4.48 (1H, d, J = 7.5 Hz, 4-H), 3.95 - 3.40 (2H, m, 2-H, NH; after D_2O-exchange: 1H, dq, J = 7.5 Hz, J = 6.5 Hz, 2-H), 3.00 - 2.60 (4H, m, pyrrolidyl-2-H and -5-H), 2.47 (3H, s, 4'-CH_3), 1.90 - 1.55 (4H, m, pyrrolidyl-3-H and -4-H), 1.34 (3H, d, J = 6.5 Hz, 2-CH_3); ^{13}C-nmr: δ (ppm) 165.7 (C=O), 144.4, 143.5, 129.6*, 129.3, 129.0*, 127.7, 127.4, 121.9, 117.6, 113.6 (arom. C), 72.2 (3-C), 61.5 (4-C), 51.7 (2-C), 48.6* (pyrrolidyl-2-C and -5-C), 24.0* (pyrrolidyl-3-C and -4-C), 21.5 (4'-CH_3), 18.9 (2-CH_3); ir: 1715 cm^{-1} (ν_{ester}); ms (m/z) 350 (M^+). Anal. Calcd for $C_{22}H_{26}N_2O_2$: C, 75.39; H, 7.47; N, 7.99. Found: C, 75.35; H, 7.56; N, 7.96.

2-Methyl-4-pyrrolidyl-3-(3,4,5-trimethoxybenzoyloxy)-1,2,3,4-tetrahydroquinoline (10c): Colorless oil; ^{1}H-nmr: δ (ppm) 7.46 - 6.45 (6H, m, arom. H), 5.50 (1H, t, J = 7.5 Hz, 3-H), 4.24 (1H, d, J = 7.5 Hz, 4-H), 3.90 (3H, s, 4'-OCH_3), 3.86 (6H, s, 3'- and 5'-OCH_3), 4.40 - 3.80 (1H, m, 2-H), 3.35 - 2.54 (5H, m, pyrrolidyl-2-H and -5-H, NH), 1.88 - 1.55 (4H, m, pyrrolidyl-3-H and -4-H), 1.32 (3H, d, J = 7.0 Hz, 2-CH_3); ir: 1720 cm^{-1} (ν_{ester}); ms (m/z) 426 (M^+). Anal. Calcd for $C_{24}H_{30}N_2O_5$: C, 67.58; H, 7.08; N, 6.56. Found: C, 67.36; H, 7.32; N, 6.34.

2-Methyl-3-*p*-nitrobenzoyloxy-4-pyrrolidyl-1,2,3,4-tetrahydroquinoline (10d): Yellow crystals, mp 155 - 157 °C (ether); ^{1}H-nmr: δ (ppm) = 8.33, 8.17 (4H, AB-system, J = 9.5 Hz, arom. H), 7.41 - 6.50 (4H, m, arom. H), 5.53 (1H, t, J = 7.5 Hz, 3-H), 4.30 (1H, d, J = 7.5 Hz, 4-H), 3.88 - 3.37 (2H, m, 2-H, NH), 2.88 - 2.56 (4H, m, pyrrolidyl-2-H and -5-H), 1.82 - 1.54 (4H, m, pyrrolidyl-3-H and

-4-H), 1.33 (3H, d, J = 7.0 Hz, 2-CH_3); ^{13}C-nmr: δ (ppm) 164.0 (C=O), 144.3, 143.3, 135.6, 130.7*, 129.4, 128.0, 123.6*, 121.3, 117.8, 113.9 (arom. C), 74.1 (3-C), 61.8 (4-C), 51.6 (2-C), 49.0* (pyrrolidyl-2-C and -5-C), 24.1* (pyrrolidyl-3-C and -4-C), 19.2 (2-CH_3); ir: 1720 (ν_{ester}), 1530, 1340 cm^{-1} (ν_{NO_2}); ms (m/z) 381 (M^+). Anal. Calcd for $C_{21}H_{23}N_3O_4$: C, 66.12; H, 6.07; N, 11.01. Found: C, 66.16; H, 6.22; N, 10.96.

3-Acetoxy-2-methyl-4-pyrrolidyl-1,2,3,4-tetrahydroquinoline (10e): Spontaneously crystallizing oil, mp 120 - 122 °C; ^{1}H-nmr: δ (ppm) 7.39 - 6.42 (4H, m, arom. H), 5.25 (1H, t, J = 7.5 Hz, 3-H), 4.09 (1H, d, J = 7.5 Hz, 4-H), 3.70 - 3.20 (2H, m, 2-H, NH), 2.82 - 2.54 (4H, m, pyrrolidyl-2-H and -5-H), 2.06 (3H, s, CO-CH_3), 1.85 - 1.57 (4H, m, pyrrolidyl-3-H and -4-H), 1.24 (3H, d, J = 6.5 Hz, 2-CH_3); ir: 1720 cm^{-1} (ν_{ester}); ms (m/z) = 274 (M^+). Anal. Calcd for $C_{16}H_{22}N_2O_2$: C, 70.04; H, 8.08; N, 10.21. Found: C, 69.76; H, 8.18; N, 10.01.

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