Synthesis of Peptides Containing 1,2,3,4-Tetrahydroquinoline-2-carboxylic Acid. Part 3 (1). Cyclization of Dipeptides and Amides with Acetic Anhydride

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Treatment of protected dipeptides containing 1,2,3,4-tetrahydroquinoline-2-carboxylic acid with acetic anhydride affords only 1*H*,3*H*,5*H*-oxazolo[3,4-*a*]quinolin-3-one derivatives. The formation of *a*-acylaminomethylketones, arising from the competitive Dakin-West reaction, was generally observed when the cyclization procedure was extended to some amides of the cyclic imino acid. The preferential stabilization of one of two probable mesoionic intermediates seems to determine the preferred pathway.

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We have recently reported (1) the crystal and molecular structure of a 1*H*,3*H*,5*H*-oxazolo[3,4-*a*]quinolin-3-one derivative (**2a**) obtained from a linear tripeptide (**1a**) containing 1,2,3,4-tetrahydroquinoline-2-carboxylic acid, by treatment with acetic anhydride-sodium acetate. The mechanism of the cyclization was discussed and related to the Dakin-West reaction (2).

In order to explore the factors affecting that unexpected reaction pathway, it seemed of interest to extend the cyclization procedure to some dipeptides and amides of the above imino acid.

Treatment of *N*-benzyloxycarbonyl-(*S*)-phenylalanyl-(*R*)-1,2,3,4-tetrahydroquinoline-2-carboxylic acid (**1b**) with acetic anhydride (3) afforded two neutral isomeric compounds: on the basis of their elemental and spectroscopic data we assigned the oxazolidinone structures **2b** to that obtained in higher yield and **3b** to the other one.

Scheme I

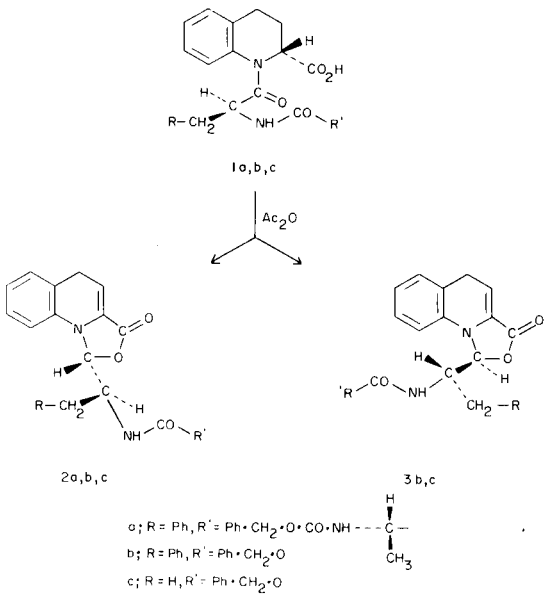

Table 1

Cyclization of Dipeptides Containing (*R*)-1,2,3,4-Tetrahydroquinoline-2-carboxylic Acid

Starting Dipeptide	Products Isolated and Yields (%) (a)			
1b	**2b**	49.8	**3b**	19.7
1c	**2c**	61.15	**3c**	10.35

(a) Yields calculated from weights of pure chromatographic fractions.

Cyclization of *N*-benzyloxycarbonyl-(*S*)-alanyl-(*R*)-1,-2,3,4-tetrahydroquinoline-2-carboxylic acid (**1c**) as above gave a similar reaction mixture (see Table 1). In the ir spectra all these reaction products show a characteristic strong absorption in the region 1792-1775 cm^{-1} due to the oxazolidinone carbonyl group. The structural assignment for diastereomeric 1*H*,3*H*,5*H*-oxazolo[3,4-*a*]-quinolin-3-one derivatives **2b**, **3b** and **2c**, **3c** was made by comparing their ^1H nmr spectra with that of **2a**, whose configuration was unequivocally determined in the previous work (1) (see Table 2).

Except for the lack of signals due to the alanine residue, **2b** shows a resonance pattern close to that of **2a**. The main differences concern the chemical shift of the phenylalanine methine group and that of the corresponding amide proton. A first noteworthy feature in the spectrum of **3b** is the absence of the high field signal attributed (1) to the C-9 proton, which is conversely, not separated from the other aromatic protons. Furthermore, the oxazolidinone proton occurs downfield relative to the vinyl proton [in the spectra of **2a** and **2b** these signals are superimposed]. Again the methylene protons of the phenylalanine residue appear in the spectrum of **3b** at δ 2.64 and 3.0 while the corresponding shifts in **2a** and **2b** are very similar. Finally, **2c** and **3c** show resonance patterns (typical of the characteristic vinyl, oxazolidinone and aromatic absorptions) similar to those of **2a,b** and **3b**, respectively.

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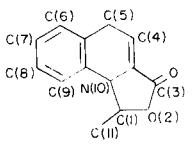
Table 2

^{1}H Nmr Data (δ) for Diastereomeric 1*H*,3*H*,5*H*-Oxazolo[3,4-*a*]quinolin-3-one Derivatives and **2a** (a)

Compound No.	5-H_2 (b)	4-H (c)	1-H	9-H (d)	Other Signals
2b	3.5	5.55	5.54	6.14	2.99 (2H, three lines, Ph-CH_2-CH), 4.56 (1H, m, Ph-CH_2-C*H*), 4.87-5.07 [3H, Ph-CH_2-O (at 4.99, s), superimposed on NH signal, removed in deuterium oxide], 6.89-7.37 (13H, m, aromatic)
3b	3.58	5.63	5.87		2.64 and 3.0 (2H, A and B. of ABX, J_{AB} = 15 Hz, J_{AX} = 10 Hz, J_{BX} = 5 Hz, Ph-CH_2-CH), 4.6 (1H, m, Ph-CH_2-C*H*), 5.0-5.2 [3H, Ph-CH_2-O (at 5.07, s), superimposed on NH signal, removed in deuterium oxide], 6.93-7.4 (14H, m, aromatic)
2c	3.52	5.57	5.6	6.52	1.31 (3H, d, J = 7 Hz, CH_3), 4.42 (1H, m, simplified to a quartet by exchange with deuterium oxide, C*H*-CH_3), 4.8 (1H, br s, removed in deuterium oxide,NH), 5.03 (2H, br s, Ph-CH_2-O), 6.93-7.43 (8H, m, aromatic)
3c	3.66	5.64	5.81		1.13 (3H, d, J = 7 Hz, CH_3), 4.37 (1H, m, simplified to a quartet by exchange with deuterium oxide,C*H*-CH_3), 5.08 (1H, br d, removed in deuterium oxide,NH), 5.16 (2H, s, Ph-CH_2-O), 6.9-7.5 (9H, m, aromatic)
2a	3.57	5.56	5.56	6.2	2.97 (2H, d, J = 8.2 Hz, Ph-CH_2-CH), 4.9 (1H, m, simplified to a triplet by exchange with deuterium oxide,Ph-CH_2-C*H*), 6.8 (1H, br d, removed in deuterium oxide,N*H*-CO-CH)

(a) Data from previous work. (b) The allylic CH_2 (5-H_2) appears as a doublet (J = 4.5 Hz). (c) The vinylic triplet (4-H) (J = 4.5 Hz) in **2a,b,c** is superimposed on the oxazolidinone signal (1-H), which in **3b** and **3c** appears as a singlet. (d) The 9-H proton in **2a,b** occurs as a multiplet and in **2c** as an apparent doublet, while in **3b,c** it is not separated from the other aromatic protons.



1*H*,3*H*,5*H*-oxazolo[3,4-*a*]quinoline system.

On the basis of these ^{1}H nmr data it seems reasonable to assume that the different preferential distribution of the conformers in each couple of diastereoisomers, which principally affects the chemical shifts of the corresponding groups (4), reflects the relative sequence of the configurations at C-1 and C-11. In the absence of a chemical confirmation we tentatively assign to the C-1 and C-11 asymmetric carbons in **2b** and **2c** the same configuration (*R* and *S* respectively) found in **2a** (1). As a consequence the configuration of the oxazolidinone derivatives **3b** and **3c**, obtained in lower yield, should be *S* and *S*. This assignment can be supported by the following observation: it seems unlikely that, in the absence of equilibration of **3b** and **3c** into **2b** and **2c** under the same reaction conditions, a drastic change in steric control of asymmetric induction may occur turning from **1a** to **1b** and **1c**.

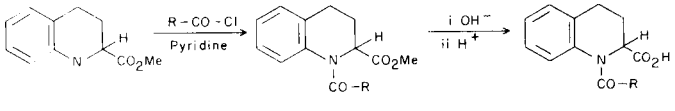
The main information regarding the orientation of the side chain bonded to C-1 is obtained from the chemical shift of the C-9 proton. Its high field position in **2a** and **2b** arises from the π-electron resonance of the >N-substituent (5) and to some extent may be due to the magnetic shielding effect of phenylalanine aromatic ring (1). In fact, a δ 6.52 value was found for **2c**. The lack of this upfield signal in the spectra of **3b** and **3c** may be due to a deshielding effect of the amide carbonyl group which, in the preferred conformations, should lie close to the hydrogen at C-9. From these data it appears that the orientation of the side chain in **3b** and **3c** differs from that adopted by **2b** and **2c**, which is probably closer to that found for **2a** (1).

Cyclization of *N*-benzyloxycarbonyl-(*S*)-phenylalanyl-(*S*)-1,2,3,4-tetrahydroquinoline-2-carboxylic acid and *N*-benzyloxycarbonyl(*S*)-alanyl-(*S*)-1,2,3,4-tetrahydroquinoline-2-carboxylic acid, afforded mixtures identical with those obtained from the corresponding diastereomeric dipeptides **1b** and **1c**. This result shows that the relative configuration of the cyclic imino acid in the starting dipeptides has no influence on the reaction pathway. Cyclization of *N*-benzyloxycarbonylglycyl-(*R*,*S*)-1,2,3,4-tetrahydroquinoline-2-carboxylic acid gave, as expected, only one 1*H*,3*H*,5*H*-oxazolo[3,4-*a*]quinolin-3-one derivative. The presence of 1,2,3,4-tetrahydroquinoline-2-carboxylic acid appears to be determinant for the observed reaction outcome, since analogous oxazolidinone der-

ivatives could not be isolated starting from dipeptides containing other imino acids. Thus *N*-benzyloxycarbonylglycyl-(*S*)-proline afforded, under the usual reaction conditions, 4-(benzyloxycarbonyl)-(*S*)-3,6-dioxo-1,2-pyrrolidinopiperazine in low yield, and, as the main product, a mixed anhydride (detected *via* ir and ^{1}H nmr), which after chromatographic separation on silica, gave the starting dipeptide. A complex mixture, which was not further examined, was instead obtained, in addition to the starting material, from *N*-benzyloxycarbonylglycyl-2-anilino-(*R*,*S*)-*n*-butyric acid.

In order to examine whether the nature of the *N*-acyl group may play a role in the formation of the cyclic compounds isolated starting from peptides containing 1,2,3,4-tetrahydroquinoline-2-carboxylic acid, several amides of this imino acid were synthesised.

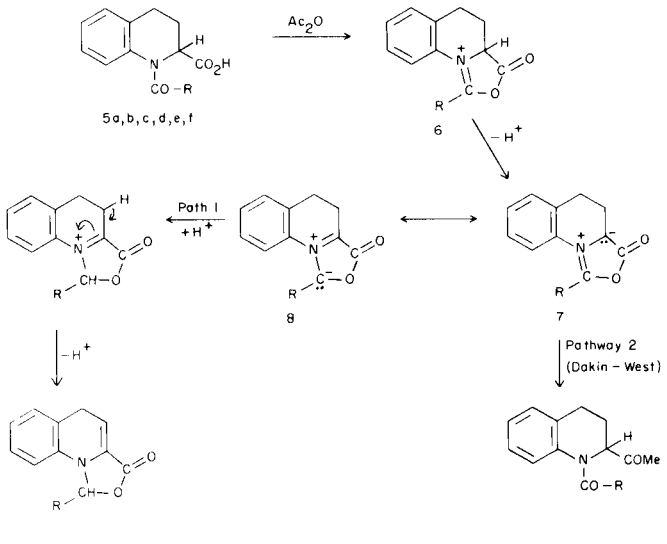
Scheme 2



4a,b,c,d,e,f 5a,b,c,d,e,f

a; R = Ph
b; R = p-OMe·C$_6$H$_4$
c; R = p-NO$_2$·C$_6$H$_4$
d; R = Me
e; R = 
f; R = (Me)$_3$C

Scheme 3



5a,b,c,d,e,f 6 8 7 9a,b,c,d,e,f 10a,b,d,e,f

a; R = Ph
b; R = p-OMe·C$_6$H$_4$
c; R = p-NO$_2$·C$_6$H$_4$
d; R = Me
e; R = 
f; R = (Me)$_3$C

Analytical, physical, and spectral data for *N*-acyl-1,2,3,4-tetrahydroquinoline-2-carboxylic acids and the corresponding methyl esters are reported in Tables 3 and 4.

Interestingly, treatment of both aromatic and aliphatic amides with acetic anhydride afforded, in most cases, together with the expected oxazolidinone derivatives, *N*-acyl-2-acetyl-1,2,3,4-tetrahydroquinolines arising from the competitive Dakin-West reaction (2) (Scheme 3).

Analytical, physical, and spectral data for racemic 1*H*,3*H*,5*H*-oxazolo[3,4-*a*]quinolin-3-one derivatives and corresponding *N*-acyl-2-acetyl-1,2,3,4-tetrahydroquinolines are reported in Tables 5,6, and 7.

As shown in Table 5, a 1*H*,3*H*,5*H*-oxazolo[3,4-*a*]-quinolin-3-one derivative (**9a**) was obtained in higher yield in comparison with the *N*-benzoylmethylketone (**10a**) (6). Introduction of an electron-releasing group on the aromatic ring, as in *p*-methoxybenzoyl-1,2,3,4-tetrahydroquinoline-2-carboxylic acid (**5b**), enhanced the yield of the *N*-acylmethylketone (**10b**), while a corresponding derivative could not be detected in the case of *p*-nitrobenzoyl-1,2,3,4-tetrahydroquinoline-2-carboxylic acid (**5c**).

A more drastic change in the ratio of the oxazolidinone derivative to the *N*-acylmethylketone (**9**/**10**) was observed going from **5d** to **5f**. An attractive explanation of our results would be that the probable driving force for this reaction is the preferential stabilization of one of two mesomeric intermediates **7** and **8** arising from an oxazolonium cation **6** (Scheme 3). It seems thus reasonable to assume that the presence of an electron-withdrawing group would favour the formation of **9** (path 1), while an electron-releasing group would increase the importance of the resonance structure **7** and lead preferentially to an *N*-acylmethylketone **10** (path 2). In this view it is noteworthy that *N*-formyl-1,2,3,4-tetrahydroquinoline-2-carboxylic acid failed to react at all.

Since the reaction results in the series of aliphatic amides were found opposite to that expected from the inductive electron release by alkyl R groups, it would not be unfair to point out the primary importance of the isovalent hyperconjugation in the stabilization of the mesoionic intermediate **7**. In fact, the *N*-acetylmethylketone **10d** was the main product obtained from *N*-acetyl-1,2,3,4-tetrahydroquinoline-2-carboxylic acid (**5d**) while the ratio (**9**/**10**) was found reversed in the case of the pivaloyl derivative **5f**. Intermediate behaviour was exhibited by **5e** (8).

In this connection, the exclusive formation of 1*H*,-3*H*,5*H*-oxazolo[3,4-*a*]quinolin-3-one derivatives from the peptides containing 1,2,3,4-tetrahydroquinoline-2-carboxylic acid may be further rationalised. It appears likely that, because of an adjacent -NH-CO- group, the hyperconjugative stabilization of **7** by a -CH< (as in the cyclization of **1a,b,c**) or a -CH$_2$- group (as in the case

Table 3

Analytical Data for *N*-Acyl-1,2,3,4-tetrahydroquinoline-2-carboxylic Acids and Melting points of the Corresponding Methyl Esters

Compound No.	M.p. °C	Formula	Calcd. % C	H	N	Found % C	H	N
4a	108-109 (a)							
5a	180-181 (b)							
4b	150-151 (c)							
5b	198-200 (d)	$C_8H_{17}NO_4$	69.45	5.5	4.5	69.55	5.6	4.4
4c	138-139 (d)							
5c	98-99 (e)	$C_{17}H_{14}N_2O_5 \cdot H_2O$	59.3	4.7	8.15	59.45	4.65	7.9
4d	102-103 (c)							
5d	174-175 (f)							
4e	50-55 (g)							
5e	154-155 (h)	$C_{17}H_{21}NO_3$	71.05	7.4	4.85	70.95	7.2	4.85
4f	59-60 (i)							
5f	127-129 (i)	$C_{15}H_{19}NO_3$	68.95	7.35	5.35	69.05	7.3	5.35

(a) Lit. (9) m.p. 111-112°. (b) Lit. (9) m.p. 184-186°. (c) From ether. (d) From ethyl acetate. (e) From ethyl acetate-ether. (f) Lit. (10) m.p. 175-176°. (g) Obtained as an oil which slowly crystallized. (h) From methanol-ether (i) From ether-light petroleum.

of *N*-benzyloxycarbonylglycyl-(*R*,*S*)-1,2,3,4-tetrahydroquinoline-2-carboxylic acid) does not occur. Accordingly, treatment of the dipeptide *N*-benzyloxycarbonyl-β-alanyl-(*R*,*S*)-1,2,3,4-tetrahydroquinoline-2-carboxylic acid with acetic anhydride afforded both the corresponding oxazolidinone derivative and the *N*-acylmethylketone in a 0.87 molar ratio.

In conclusion, an overall analysis of our results seems to indicate that steric effects of the R substituents do not play an important role in determining the preferred reaction pathway, which appears to be strongly influenced by electronic resonance effects.

EXPERIMENTAL

Melting points were determined with a Büchi oil bath apparatus and are uncorrected. Optical rotations were taken at 20° with a Schmidt-Haensch polarimeter (1 dm cell). Ir spectra were recorded with Perkin-Elmer 521 and 177 spectrophotometers. The ^1H nmr spectra were measured with a Varian EM-390 spectrometer using, unless otherwise specified, deuteriochloroform as the solvent (TMS as the internal standard). Woelm alumina and Grace silica gel (Type 9, 200-400 mesh) were used for column chromatography; preparative layer chromatography (plc) was carried out with Merck HF_{254} silica gel (layers 0.5 mm thick). Light petroleum refers to the 40-60° b.p. fraction. The drying agent used was sodium sulphate.

General Procedure for the Synthesis of *N*-Acyl-(*R*-*S*)-1,2,3,4-tetrahydroquinoline-2-carboxylic Acids (**5a,b,c,d,e,f**).

To a solution of (*R*,*S*)-methyl 1,2,3,4-tetrahydroquinoline-2-carboxylate in anhydrous pyridine cooled to 0°, the appropriate acid chloride (neat or in dry ether solution) was added (molar ratio ester to acid chloride 1:2). The mixture was left at room temperature in the dark for 4-6 hours (in the case of the pivaloyl derivative it was refluxed for 1 hour), then poured into ice-water and extracted with ethyl acetate. The organic layers were washed with 2*N* hydrochloric acid, aqueous sodium bicarbonate, and water, dried and evaporated. The residues were purified by column chromatography and crystallization to afford methyl *N*acyl-(*R*,*S*)-1,2,3,4-tetrahydroquinoline-2-carboxylates (**4a,b,c,d,e,f**). Methanolic alkaline hydrolysis of the above esters, as described for **1b** (11), gave the corresponding *N*-acyl-(*R*,*S*)-1,2,3,4-tetrahydroquinoline-2-carboxylic acids (**5a,b,c,d,e,f**).

General Conditions for the Reaction of Dipeptides and Amides Containing 1,2,3,4-Tetrahydroquinoline-2-carboxylic Acid with Acetic Anhydride.

The dipeptide (or amide) was heated at 100° for 1 hour in acetic anhydride (5 ml. *per* mmole) and the solution was evaporated under vacuum to dryness. Chloroform was added and the organic phase was washed with aqueous sodium bicarbonate and water, dried and evaporated under reduced pressure. All the separations of the products arising from the amides were performed by plc [benzene-ethyl acetate (9:1) as eluant].

Cyclization of **1b**.

N-Benzyloxycarbonyl-(*S*)-phenylalanyl-(*R*)-1,2,3,4-tetrahydroquinoline-2-carboxylic acid (**1b**) (11) (1 g.) gave after the usual workup a residue which was chromatographed on silica gel (plc) [benzene-ether (9:1) as eluant] to give the less polar 1*H*,3*H*,5*H*-oxazolo[3,4-*a*]quinolin-3-one derivative (**3b**) (0.18 g.), m.p. 137-138° dec. (from ether); $[\alpha]_D$ + 12° (c 1.0, chloroform); ir (potassium bromide): 3340, 1782, 1705, 1688 cm^{-1}, and the more polar diastereoisomer (**2b**) (0.46 g.), m.p. 173-176° (from ether); $[\alpha]_D$ -1.3° (c, 4.0, chloroform); ir (potassium bromide): 3342, 1755, 1715, 1675 cm^{-1}.

Anal. Calcd. for $C_{27}H_{24}N_2O_4$: C, 73.6; H, 5.5; N, 6.35. Found: C, 73.35; H, 5.65; N, 6.25 (**3b**) and C, 73.45; H, 5.65; N, 6.3 (**2b**).

N-Benzyloxycarbonyl-(*S*)-alanyl-(*R*)-1,2,3,4-tetrahydroquinoline-2-carboxylic Acid (**1c**) and its Diastereoisomer.

By following the procedure previously described for the methyl ester of **1b** (11), an oily residue (6.23 g.) was obtained starting from *N*-benzyloxycarbonyl-(*S*)-alanine (5.01 g.) and (±)-methyl 1,2,3,4-tetrahydroquinoline-2-carboxylate (2.88 g.). The residue was chromatographed on alumina (Brockmann IV; 250 g.). Elution with light petroleum-ether (7:3) and further purification on silica (plc) [benzene-ethyl acetate (9:1) as eluant] gave the

Table 4

Spectral Data for *N*-Acyl-1,2,3,4-tetrahydroquinoline-2-carboxylic Acids and the Corresponding Methyl Esters

Compound No.	^{1}H Nmr (δ) (g) CH_2-CH_2 (a)	CH-CO_2 (b)	Ar (4H)	OH (c)	CO_2-CH_3 (c)	R	Ir, Cm^{-1} (f)
4a	1.67-2.9	5.12	6.53-7.45		3.7	6.53-7.45 (5H, m, aromatic)	1755 and 1648
5a	1.7-2.9	5.13	6.5-7.4	8.74		6.5-7.4 (5H, m, aromatic)	1715 and 1645
4b	1.65-2.85	5.09	6.6-7.3		3.71 (e)	3.75 (e) (3H, s, OCH_3), 6.72 and 7.31 (4H, two d, aromatic)	1750 and 1650
5b	1.45-2.85	4.84	6.45-7.35	8.3-13 (d)		3.73 (3H, s, OCH_3), 6.82 and 7.23 (4H, two d, aromatic)	1718 and 1642
4c	1.7-2.95	5.16	6.5-7.33		3.75	5.72 and 8.11 (4H, two d, aromatic)	1758 and 1652
5c	1.67-2.93	5.13	6.44-7.3	9.39		7.49 and 8.1 (4H, two d, aromatic)	1748 and 1630
4d	1.45-2.85	5.2	7.1-7.32		3.68	2.23 (3H, s, CH_3)	1750 and 1660
5d	1.55-2.83	5.15	7.1-7.3	7.53		2.22 (3H, s, CH_3)	1740 and 1605
4e	0.75-3.05	5.17	7.08-7.33		3.64	0.75-3.05 [11H, m, $(CH_2)_5CH$]	1745 and 1640
5e	0.85-3.05	5.11	7.19 (e)	9.27		0.85-3.05 [11H, m, $(CH_2)_5CH$]	1752 and 1612
4f	1.4-2.8	5.0	7.12-7.4		3.64	1.15 [9H, s, $(CH_3)_3C$]	1758 and 1640
5f	1.6-2.85	4.93	7.21 (c)	10.4		1.13 [9H, s, $(CH_3)_3C$]	1725 and 1638

(a) Two multiplets (3H, downfield m; 1H, upfield m). (b) Apparent triplets or X parts of ABX systems. (c) Singlet. (d) Very broad signal. (e) This assignment may be reversed. (f) Potassium bromide. (g) DMSO-d_6 solution for **5b**.

Table 5

Physical and Analytical Data for Racemic 1*H*,3*H*,5*H*-Oxazolo[3,4-*a*]quinolin-3-one Derivatives and the Corresponding *N*-Acyl-2-acetyl-1,2,3,4-tetrahydroquinolines

Compound No.	M.p. °C	Yield (a) (%)	Ratio 9/10	Formula	Calcd. % C	Calcd. % H	Calcd. % N	Found % C	Found % H	Found % N
9a	111-112 (b)	41.2	12.5	$C_{17}H_{13}NO_2$	77.55	5.0	5.3	77.65	5.05	5.4
10a	109-110 (c)	3.3		$C_{18}H_{17}NO_2$	77.4	6.15	5.0	77.3	6.2	5.1
9b	84-85 (d)	25.5	2.5	$C_{18}H_{15}NO_3$	73.7	5.15	4.8	73.7	5.25	4.7
10b	oil	10.1		$C_{25}H_{23}N_5O_6$ (e)	61.35	4.75	14.3	61.2	4.8	14.15
9c	oil	43.2		$C_{17}H_{12}N_2O_4$	66.25	3.9	9.1	65.75	4.3	8.55
9d	oil	3	0.08	Detected by ir and ^{1}H nmr on a plc fraction.						
10d	73-75 (c)	35.7		$C_{13}H_{15}NO_2$	71.85	6.95	6.45	71.9	7.0	6.55
9e	97-98 (d)	31.0	1.0	$C_{17}H_{19}NO_2$	75.8	7.1	5.2	75.8	7.1	5.2
10e	oil	31.0		$C_{18}H_{23}NO_2$	75.75	8.1	4.9	75.55	8.1	4.9
9f	oil	73.0	10.4	$C_{15}H_{17}NO_2 \cdot 1/4\ H_2O$	72.7	7.12	5.65	72.8	7.1	5.6
10f	oil	7.0		$C_{22}H_{25}N_5O_5$ (f)	60.1	5.75	15.95	60.0	5.7	15.7

(a) Yields calculated from weights of pure chromatographic fractions. (b) From ethyl acetate-ether. (c) From ether. (d) From ether-light petroleum. (e) Obtained as the 2,4-dinitrophenylhydrazone, m.p.152-153° dec. (f) Obtained as the 2-4-dinitrophenylhydrazone, m.p. 145-147° dec.

Table 6

Spectral Data for racemic 1*H*,3*H*,5*H*-Oxazolo[3,4-*a*]quinolin-3-one Derivatives

Compound	^{1}H Nmr (δ) 5-H_2 (a)	4-H (b)	1-H (c)	9-H (d)	Aromatic (3H)	R	Ir, Cm^{-1}
9a	3.77	5.72	6.3	6.23	6.85-7.69	6.85-7.69 (5H, m, aromatic)	1780 and 1678 (e)
9b	3.74	5.67	6.23	6.23	7.09-6.82	3.77 (3H, s, OCH_3), 7.47 and 6.96 (4H, two d, aromatic)	1788 and 1690 (e)
9c	3.75	5.74	6.38	6.15	6.87-7.17	7.75 and 8.26 (4H, two d, aromatic)	1798 and 1690 (f)
9d	3.68	5.6	5.71	6.5	6.91-7.33	1.73 (3H, d, J = 5 Hz, CH_3)	1790 and 1690 (f)
9e	3.65	5.54	5.5	6.52	6.87-7.2	0.9-2.1 [11H, m, $(CH_2)_5CH$]	1765 and 1675 (e)
9f	3.5	5.7	5.6	6.77	6.9-7.25	1.05 [9H, s, $(CH_3)_3C$]	1788 and 1684 (f)

(a) The allylic CH_2 (5-H_2) appears as a doublet (J = 4.5 Hz) for **9d,e,f** and as an apparent doublet for **9a,b,c**. (b) The vinylic signal (4-H), (t, J = 4.5 Hz) is superimposed on the 1-H signal in **9d** and **9e**. (c) The oxazolidonone proton (1-H) occurs as a singlet in **9a,b,c,f** and as a quartet (J = 5 Hz) in **9d**. (d) The 9-H signal is superimposed on 1-H in **9a,b**. It appears as a multiplet in **9a,b,c** and as an apparent doublet in **9d,e,f**. (e) Potassium bromide. (f) Chloroform solution.

Table 7

Spectral Data for Racemic *N*-Acyl-2-acetyl-1,2,3,4-tetrahydroquinolines

Compound No.	^{1}H Nmr (δ)					Ir, Cm^{-1}
	CH_3-CO (a)	CH_2-CH_2 (b)	CH-CO (c)	Aromatic (4H)	R	
10a	2.2	1.6-2.9	5.1	6.5-7.4	6.5-7.4 (5H, m, aromatic)	1722 and 1632 (d)
10b	2.19	1.55-2.9	5.06	6.5-7.4	3.77 (3H, s, OCH_3), 6.73 and 7.3 (4H, two d, aromatic)	1724 and 1632 (e)
10d	2.13	1.5-2.84	5.13	7.09-7.33	2.23 (3H, s, CH_3)	1720 and 1645 (d)
10e	2.1	0.9-3.0	5.11	7.1-7.34	0.9-3.0 [11H, m, $(CH_2)_5CH$]	1713 and 1640 (e)
10f	2.12	1.4-2.8	4.99	7.13-7.34	1.16 [9H, s, $(CH_3)_3C$]	1718 and 1634 (e)

(a) Singlet. (b) Two multiplets (3H, downfield m; 1H, upfield m). (c) Triplet (J = 8.5 Hz) for **10a,b,e**, deformed triplet for **10d,10f**. (d) Potassium bromide. (e) Chloroform solution.

starting methyl ester, $[\alpha]_D$ + 27° (c, 1.0, chloroform). Elution with light petroleum-ether (6:4 and 1:1) and successive separation on silica as above, gave the less polar methyl *N*-benzyloxycarbonyl-(*S*)-alanyl-(*R*)-1,2,3,4-tetrahydroquinoline-2-carboxylate as an oil (1.86 g.); $[\alpha]_D$ + 207° (c, 1.0, chloroform); ir (carbon tetrachloride): 3418, 1750, 1718, 1656 cm^{-1}; nmr: δ 0.97 (3H, t, J = 7 Hz,CH_3), 1.47-2.8 (4H, two m, CH_2-CH_2), 3.63 (3H, s, CH_3O-CO), 4.94-5.33 [4H, m, Ph-C*H*$_2$-O (at 5.1, s) superimposed on C*H*-CH_3 and CH-CO_2 signals], 5.72 (1H, br d, exchanged in deuterium oxide, NH), 7.1-7.58 (9H, m, aromatic), and the more polar methyl *N*-benzyloxycarbonyl-(*S*)-alanyl-(*S*)-1,2,3,4-tetrahydroquinoline-2-carboxylate (0.94 g.); $[\alpha]_D$ -130° (c, 1.0, chloroform); ir (carbon tetrachloride): 3428, 1746, 1720, 1656 cm^{-1}; nmr: δ 1.45 (3H, t, J = 7 Hz, CH_3), 1.6-2.77 (4H, two m, CH_2-CH_2), 3.67 (3H, s, CH_3O-CO), 4.8 (1H, m, simplified to a q, J = 7 Hz, by exchange with deuterium oxide, C*H*-CH_3), 4.97 (2H, s, Ph-C*H*$_2$-O), 5.07-5.44 [2H, m, CH-CO_2 (at 5.17) superimposed on NH signal which was removed in deuterium oxide], 7.11-7.43 (9H, m, aromatic). The less polar dipeptide ester, $[\alpha]_D$ + 207°, was hydrolysed as previously described for methyl ester of **1b** (11) to yield the dipeptide acid (**1c**) as an oil; $[\alpha]_D$ + 194° (c, 1.0, chloroform); ir (chloroform): 3420, 1712, 1648 cm^{-1}; nmr: δ 0.97 (3H, t, J = 7 Hz, CH_3), 1.5-2.8 (4H, m, CH_2-CH_2), 4.91-5.28 [4H, m, Ph-C*H*$_2$-O (at 5.09, s) superimposed on C*H*-CH_3 and CH-CO_2 signals], 5.83 (1H, d, exchanged in deuterium oxide, NH), 7.1-7.53 (9H, m, aromatic), 8.1 (1H, exchanged in deuterium oxide, CO_2H).

Anal. Calcd. for $C_{21}H_{22}N_2O_5 \cdot 1/2\ H_2O$: C, 64.45; H, 5.9; N, 7.15. Found: C, 64.9; H, 6.15; N, 6.75.

Hydrolysis of the more polar dipeptide ester, $[\alpha]_D$ -130°, afforded the corresponding dipeptide acid, m.p. 156° (from ethyl acetate); $[\alpha]_D$ -150° (c, 1.0, chloroform); ir (chloroform): 3420, 1712, 1645 cm^{-1}; nmr: δ 1.41 (3H, t, J = 6.5 Hz, CH_3), 1.57-2.8 (4H, two m, CH_2-CH_2), 4.76 (1H, m, simplified to a q, J = 6.5 Hz by exchange with deuterium oxide, C*H*-CH_3), 4.96 (2H, s, Ph-C*H*$_2$-O), 5.13 (1H, apparent t, CH-CO_2), 5.64 (1H, br d, removed in deuterium oxide, NH), 7.03-7.38 (9H, m, aromatic), 8.21 (1H, s, exchanged in deuterium oxide, CO_2H).

Anal. Calcd. for $C_{21}H_{22}N_2O_5$: C, 65.95; H, 5.8; N, 7.35. Found: C, 65.8; H, 5.9; N, 7.2.

Acid Catalysed Hydrolysis of the Dipeptide **1c**.

Compound **1c** was hydrolysed in concentrated hydrochloric acid-acetic acid as described for **1b** (11); acid-catalysed esterification and chromatography on silica (plc), with benzene-ethyl acetate (9:1) as eluant, gave (−)-(*R*)-methyl 1,2,3,4-tetrahydroquinoline-2-carboxylate (11), $[\alpha]_D$ -40° (c, 1.0, chloroform).

Cyclization of the Dipeptide **1c** with Acetic Anhydride.

N-Benzyloxycarbonyl-(*S*)-alanyl-(*R*)-1,2,3,4-tetrahydroquinoline-2-carboxylic acid (**1c**) (1.11 g.) gave after conventional workup a residue which was chromatographed on silica gel (plc) [benzene-ether (9:1) as eluant] to afford the less polar 1*H*,3*H*,5*H*-oxazolo-[3,4-*a*]quinolin-3-one derivative (**3c**) (0.11 g.), m.p. 110-112° dec. (from ether-hexane); $[\alpha]_D$ +63° (c, 1.0, chloroform); ir (potassium bromide): 3400, 1792, 1715, 1695 cm^{-1}, and the more polar diastereoisomer (**2c**) (0.65 g.), m.p. 144-145° dec. (from ether); $[\alpha]_D$ -8° (c, 1.0, chloroform); ir (potassium bromide): 3385, 1775, 1718, 1675 cm^{-1}.

Anal. Calcd. for $C_{21}H_{20}N_2O_4 \cdot 1/2\ H_2O$: C, 67.55; H, 5.65; N, 7.5. Found: 67.45; H, 5.5 N, 7.45 (**3c**).

Anal. Calcd. for $C_{21}H_{20}N_2O_4$: C, 69.2; H, 5.55; N, 7.7. Found: C, 69.65; H, 5.65; N, 7.85 (**2c**).

N-Benzyloxycarbonylglycyl(*R,S*)-tetrahydroquinoline-2-carboxylic Acid.

To a solution of (*R,S*)-methyl 1,2,3,4-tetrahydroquinoline-2-carboxylate (1.9 g.) in dry chloroform (100 ml.), cooled to 0°, *N*-benzyloxycarbonylglycine (2.09 g.), and *N-N'*-dicyclohexylcarbodiimide (2.06 g.) were added. The mixture was stirred for 1 hour at 0° and then for 4 hours at room temperature; the solution was separated by filtration and the solid residue washed with chloroform. The combined organic solution was washed with 2*N* hydrochloric acid, aqueous sodium bicarbonate, water, dried and evaporated. The residue (4.63 g.) was chromatographed on alumina (Brockmann IV; 185 g.); elution with ether-light petroleum (7:3) afforded pure methyl *N*-benzyloxycarbonylglycyl-(*R,S*)-1,2,3,4-tetrahydroquinoline-2-carboxylate as an oil; ir (carbon tetrachloride): 3420, 1750-1720, 1660 cm^{-1}; nmr: δ 1.43-2.83 (4H, two m, CH_2-CH_2), 3.64 (3H, s, CH_3-O-CO), 3.88 and 4.37 (2H, A and B of ABX, J_{AB} = 17.5, J_{AX} = 5.5, J_{BX} = 4 Hz, simplified to an AB quartet by exchange with deuterium oxide, CH_2-NH), 5.07 (2H, s, partially superimposed on the signal at 5.22, Ph-CH_2-O), 5.22 (1H, apparent t, CH-CO_2), 5.67 (1H, br s, removed in deuterium oxide, NH), 7.14-7.43 (9H, m, aromatic).

Anal. Calcd. for $C_{21}H_{22}N_2O_5$: C, 65.95; H, 5.8; N, 7.35. Found: C, 65.7; H, 5.9; N, 7.2.

Methanolic alkaline hydrolysis of the above dipeptide methyl ester gave nearly homogeneous *N*-benzyloxycarbonylglycyl-(*R,S*)-1,2,3,4-tetrahydroquinoline-2-carboxylic acid as an oil, which was further purified by column chromatography (silica 1:100) with ethyl acetate as eluant; ir (chloroform): 3410, 1715, 1645 cm^{-1}; nmr: δ 1.4-2.77 (4H, two m, CH_2-CH_2), 3.89 and 4.32 (2H, A and B of ABX, J_{AB} = 17.5, J_{AX} = 5.5, J_{BX} = 4 Hz, simplified to an AB quartet by exchange with deuterium oxide, CH_2-NH), 5.0-5.28 [3H, m, Ph-CH_2-O (at 5.04, s) superimposed on CH-CO_2], 5.81 (1H, broad signal, exchanged in deuterium oxide, NH), 7.06-7.37 (9H, m, aromatic), 7.5 (1H, s, exchanged in deuterium oxide, CO_2H).

Anal. Calcd. for $C_{20}H_{20}N_2O_5 \cdot 1/2\ H_2O$: C, 63.65; H, 5.6; N, 7.4. Found: C, 64.15; H, 5.95; N, 6.95.

Cyclization of *N*-Benzyloxycarbonylglycyl(*R,S*)-1,2,3,4-tetrahydroquinoline-2-carboxylic Acid.

Usual treatment of the above compound (0.93 g.) with acetic anhydride gave a residue which, after chromatography on silica (plc) [benzene-ethyl acetate (8:2) as eluant], yielded the corresponding 1*H*,3*H*,5*H*-oxazolo[3,4-*a*]quinolin-3-one derivative (0.4 g.) as an oil; ir (chloroform): 3440, 1788, 1715, 1688 cm^{-1}; nmr: δ 3.27 (1H, m, simplified to a dd by exchange with deuterium oxide, C*H*-NH), 3.62 (2H, d, J = 4.5 Hz, CH_2-CH=C), 4.02 (1H, m, simplified to a br d by exchange with deuterium oxide, C*H*-NH), 5.13 (2H, s, Ph-CH_2-O), 5.4 (1H, broad signal, removed in deuterium oxide, NH), 5.63 [2H, vinyl (t, J = 4.5 Hz) superimposed on N-CH-O signal], 6.73-7.44 (9H, m, aromatic).

N-Formyl-(*R,S*)-1,2,3,4-tetrahydroquinoline-2-carboxylic Acid.

(*R,S*)-Methyl 1,2,3,4-tetrahydroquinoline-2-carboxylate (1.78 g.) and 1.03 ml. of 99% formic acid were refluxed for 24 hours in dry benzene (50 ml.), water being collected in a Dean-Stark trap. An additional 1.03 ml. of formic acid was added and the mixture was refluxed for another day. The organic solution was washed with water to neutrality, dried and evaporated under reduced pressure. The oily residue was chromatographed on alumina (Brockmann IV; 116 g.); elution with light petroleum-ether (2:1 and 1:1) gave (*R,S*)-methyl *N*-formyl-1,2,3,4-tetrahydroquinoline-2-carboxylate (1.86 g.), m.p. 46.5-47.5° (from ether-light petroleum); ir (potassium bromide): 1738, 1660, 1578 cm^{-1}; nmr: δ 2.03-2.87 (4H, two m, CH_2-CH_2), 3.7 (3H, s, CH_3-O-CO), 5.1 (1H, t, J = 6.5 Hz, CH-CO_2), 7.07-7.33 (4H, m, aromatic), 8.87 (1H, s, H-CO).

Anal. Calcd. for $C_{12}H_{13}NO_3$: C, 65.75; H, 6.0; N, 6.4. Found: C, 65.75; H, 6.1; N, 6.25.

Methanolic alkaline hydrolysis afforded *N*-formyl-(*R,S*)-1,2,3,4-tetrahydroquinoline-2-carboxylic acid, m.p. 178° (from ethyl acetate); ir (potassium bromide): 1730, 1610, 1573 cm^{-1}; nmr: δ 2.04-2.91 (4H, two m, CH_2-CH_2), 5.04 (1H, t, J = 6.5 Hz, CH-CO_2), 7.07-7.5 (4H, m, aromatic), 8.94 (1H, s, H-CO).

Anal. Calcd. for $C_{11}H_{11}NO_3$: C, 64.4; H, 5.4; N, 6.85. Found: C, 64.5; H, 5.5; N, 6.75.

N-Benzyloxycarbonylglycyl-2-anilino-(*R,S*)-*n*-butyric Acid.

N-Benzyloxycarbonylglycine (3 g.) in dry ether (20 ml.) and phosphorus pentachloride (3.3 g.) were stirred at 0° for 20 minutes. The filtered solution was added to ethyl 2-anilino-(*R,S*)-*n*-butyrate (3 g.) in dry pyridine (10 ml.). The mixture was left at room temperature for 3 hours. Usual workup gave a residue (3.39 g.) which was chromatographed on silica gel (100 g.) Elution with benzene-ether (9:1) gave the dipeptide ester (0.75 g.) as an oil; ir (carbon tetrachloride): 3428, 1742, 1678 cm^{-1}; nmr: δ 0.93 (3H, t, J = 7 Hz, CH_3-CH_2-CH), 1.27 (3H, t, J = 7 Hz, CH_3-CH_2-O-CO), 1.75 (2H, m, CH_2-CH), 3.67 (2H, AB part of ABX system, simplified to an AB quartet by exchange with deuterium oxide, CH_2-NH), 4.2 (2H, q, J = 7 Hz, CH_2-O-CO), 4.73 (1H, X part of ABX system, C*H*-CH_2), 5.05 (2H, s, Ph-CH_2-O), 5.63 (1H, broad signal, NH, removed in deuterium oxide), 7.27-7.5 (9H, m, aromatic).

Anal. Calcd. for $C_{22}H_{26}N_2O_5$: C, 66.3; H, 6.6; N, 7.05. Found: C, 66.2; H, 6.65; N, 7.05.

Methanolic alkaline hydrolysis gave *N*-benzyloxycarbonylglycyl-2-anilino-(*R,S*)-*n*-butyric acid as an oil; ir (chloroform): 3425, 1725, 1670 cm^{-1}; nmr: δ 0.93 (3H, t, J = 7 Hz, CH_3), 1.8 (2H, m, CH_2-CH_3), 3.69 (2H, d, J = 5 Hz, which collapsed to a singlet after addition of deuterium oxide, CH_2-NH), 4.58 (1H, X part of ABX system, C*H*-CH_2), 5.05 (2H, s, Ph-CH_2-O), 6.02 (1H, unresolved t, exchanged in deuterium oxide, NH), 7.22-7.48 (9H, m, aromatic), 9.13 (1H, s, exchanged in deuterium oxide, CO_2H).

Anal. Calcd. for $C_{20}H_{22}N_2O_5$: C, 64.85; H, 6.0; N, 7.55. Found: C, 64.75; H, 5.95; N, 7.45.

Reaction of *N*-benzyloxycarbonylglycyl-(*S*)-proline with Acetic Anhydride.

The solution of the dipeptide acid (1 g.) in acetic anhydride (16.6 ml.) was heated at 100° for 1 hour. In the residue (1.1 g.) a mixed anhydride was detected as the major product; ir (chloroform): 1820, 1750 cm^{-1}; nmr: δ 2.17 (3H, s, CH_3-CO_2). The oil was chromatographed on silica gel (119 g.). Elution with ethyl acetate and ethyl acetate-acetic acid (9:1) and partition between ethyl acetate and sodium bicarbonate gave a neutral fraction (53 mg.) from which 4-(benzyloxycarbonyl)-(*S*)-3,6-dioxo-1,2-pyrrolidinopiperazine (33 mg.), m.p. 107-108° (from ethyl acetate-light petroleum); $[\alpha]_D$ −108° (c, 0.8, ethyl acetate) [lit.(12) m.p. 110-111.5°, $[\alpha]_D$ −109.5 (c 1.0, ethyl acetate)], was isolated by plc (ethyl acetate as eluant). The aqueous basic solution gave, after acidification with 2*N* hydrochloric acid, the starting dipeptide (0.82 g.).

N-Benzyloxycarbonyl-β-alanyl-(*R,S*)-1,2,3,4-tetrahydroquinoline-2-carboxylic Acid.

Methyl *N*-benzyloxycarbonyl-β-alanyl-(*R,S*)-1,2,3,4-tetrahydro-

quinoline-2-carboxylate was prepared as the methyl ester of **1b** (11) except that ethyl acetate was used for the extraction. From (*R,S*)-methyl 1,2,3,4-tetrahydroquinoline-2-carboxylate (1.5 g.) and *N*-benzyloxycarbonyl-β-alanine (13) (2.6 g.), an oily residue (3.2 g.) was obtained. This was chromatographed on alumina (Brockmann IV; 128 g.); elution with light petroleum-ether (1:1) afforded the dipeptide methyl ester (1.25 g.), m.p. 118-119° (from ether); ir (potassium bromide): 3325, 1758, 1752, 1690 cm^{-1}; nmr: δ 1.43-3.11 (6H, m, CH_2-CH_2-CH and CH_2-CO), 3.47 (2H, m, CH_2-N), 3.64 (3H, s, CH_3-O-CO), 5.03 (2H, s, Ph-CH_2-O, partially superimposed on the signal at 5.16), 5.16 (1H, CH-CO_2), 5.62 (1H, broad signal, removed in deuterium oxide, NH), 7.09-7.38 (9H, m, aromatic). Methanolic alkaline hydrolysis afforded *N*-benzyloxycarbonyl-β-alanyl-(*R,S*)-1,2,3,4-tetrahydroquinoline-2-carboxylic acid, m.p. 144-145° (from ether); ir (potassium bromide): 3348, 1728, 1715, 1695 cm^{-1}; nmr: δ 1.47-3.03 (6H, m, CH_2-CH_2-CH and CH_2-CH), 3.42 (2H, m, CH_2-N), 5.01 (2H, s, Ph-CH_2-O, partially superimposed on the signal at 5.09), 5.09 (1H, CH-CO_2), 5.69 (1H, broad signal, NH), 7.09-7.41 (9H, m, aromatic), 8.79 (1H, s, CO_2H).

Anal. Calcd. for $C_{21}H_{22}N_2O_5$: C, 65.95; H, 5.8; N, 7.35. Found: C, 65.85; H, 5.8; N, 7.25.

Reaction of *N*-Benzyloxycarbonyl-β-alanyl-(*R,S*)-1,2,3,4-tetrahydroquinoline-2-carboxylic Acid with Acetic Anhydride.

The above dipeptide acid (0.74 g.) after usual treatment, gave an oily residue (0.75 g.) which was chromatographed on plc [benzene-ethyl acetate (8:2) as eluant] to afford the corresponding 1*H*,3*H*,5*H*-oxazolo[3,4-*a*]quinolin-3-one derivative (0.1 g.) as an oil; ir (chloroform): 3458, 1795, 1725, 1690 cm^{-1}; nmr: δ 1.76-2.73 (2H, m, CH_2-CH_2-N), 3.43 (2H, m, CH_2-N), 3.6 (2H, d, J = 4.5 Hz, CH_2-CH=C), 5.07 (2H, s, Ph-CH_2-O), 5.27 (1H, unresolved t, NH), 5.59 [2H, m, vinyl (t, J = 4.5 Hz) superimposed on N-CH-O], 6.45 (1H, apparent d, aromatic), 6.93-7.48 (8H, m, aromatic), and the more polar *N*-benzyloxycarbonyl-β-alanyl-(*R,S*)-1,2,3,4-tetrahydro-2-acetylquinoline (0.12 g.), m.p. 103-104° (from ether); ir (potassium bromide): 3315, 1720, 1688, 1655 cm^{-1}; nmr: δ 1.37-3.07 [9H, CH_3-CO (at 2.09, s) superimposed on CH_2-CH_2-CH and CH_2-CO multiplets], 3.46 (2H, m, CH_2-N), 5.03 (3H, m, Ph-CH_2-O, superimposed on CH-CO-CH_3 signal), 5.6 (1H, broad signal, NH), 7.08-7.44 (9H, m, aromatic).

Anal. Calcd. for $C_{21}H_{20}N_2O_4$: C, 69.2; H, 5.55; N, 7.7. Found: C, 69.15; H, 5.6; N, 7.5.

Anal. Calcd. for $C_{22}H_{24}N_2O_4$: C, 69.45; H, 6.35; N, 7.35. Found: C, 69.3; H, 6.45; N, 7.5.

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