SYNTHESIS OF 4-SUBSTITUTED 11-PHENYL-1,2,3,4-TETRAHYDRO-5H-AZEPINO[3,4-b]QUINOLIN-5-ONE DERIVATIVES AS POTENTIAL PERIPHERAL BENZODIAZEPINE-RECEPTOR LIGANDS

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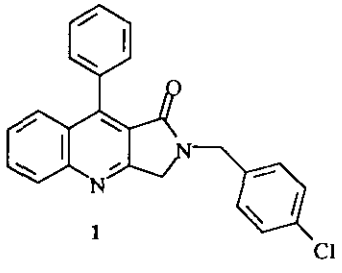
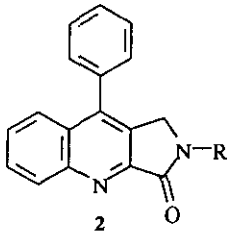
Abstract - The synthesis of semirigid analogs of PK 11195, the highly specific peripheral benzodiazepine-receptor ligand, is reported. Compound (4) underwent the Wittig reaction with acetaldehyde to give olefin (7) which after allylic bromination was aminated to give the ω-amino esters (10a-c). These compounds were then hydrogenated and cyclized in boiling toluene with DMAP as catalyst. The standard procedure failed in the case of compound (10b), thus other cyclization procedures were examined.

The synthesis of conformationally constrained derivatives of biologically active compounds represents a promising strategy to obtain more active and selective compounds and/or to define the bioactive conformation of flexible compounds.[1] Recently, we have successfully applied this strategy in the search of new serotonin 5-HT_3 receptor ligands.[2] Furthermore, in the effort to elucidate the structural determinants in the interaction of compound (1)[3] with the peripheral benzodiazepine-receptor, we synthesized compounds (2a-c)[4] which are closely related to 1 and could be regarded as conformationally constrained derivatives of PK 11195, the prototypical peripheral benzodiazepine-receptor ligand. As an extension of our previous studies we wish now to report on the synthesis of compounds (3a-c) as semirigid analogs of the aforementioned PK 11195.

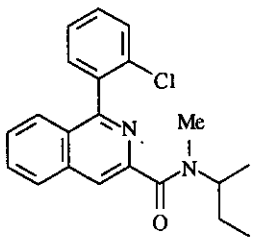


1

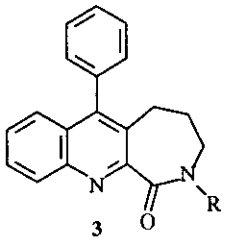


2

a : R = CH_2-Ph
b : R = CH_2-(p-ClC_6H_4)
c : R = sec-Bu



PK 11195



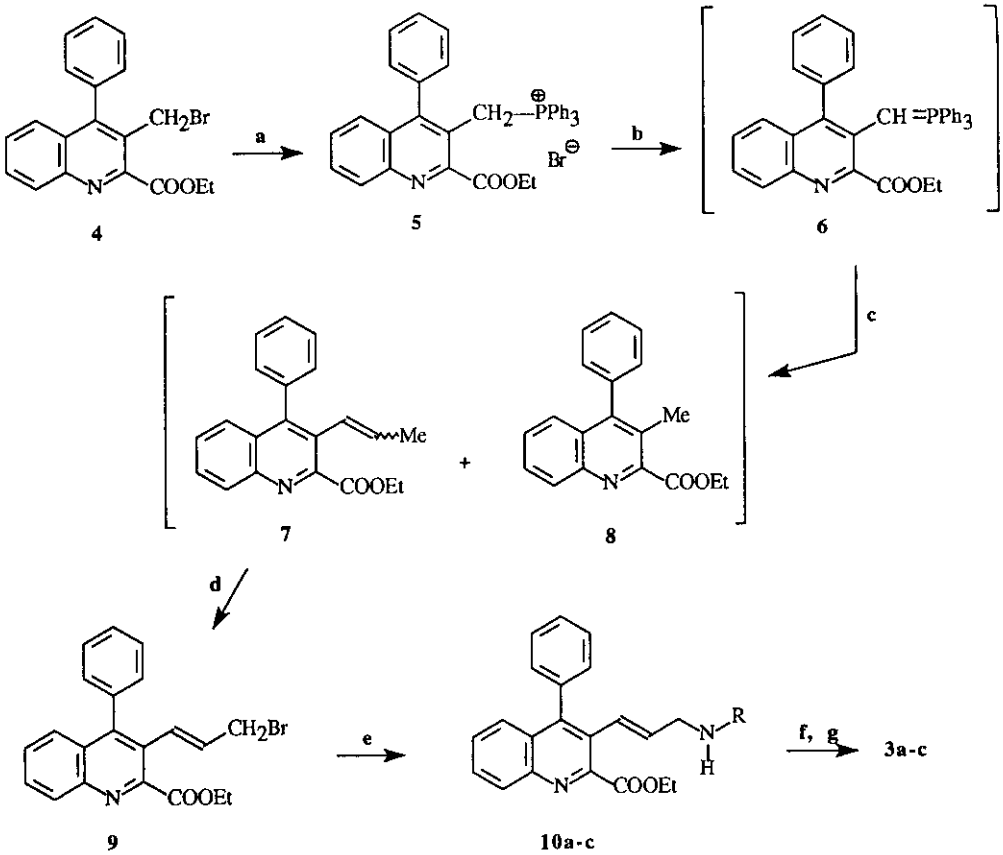
3

a : R = CH_2-Ph
b : R = sec-Bu
c : R = Me

In our opinion compounds (3a-c) should constitute a useful probe in determining the bioactive conformation of the amide moiety in the interaction with peripheral benzodiazepine receptors.

The title compounds were prepared from 3-bromomethyl-2-ethoxycarbonyl-4-phenylquinoline (4) as outlined in Scheme 1.

Scheme 1

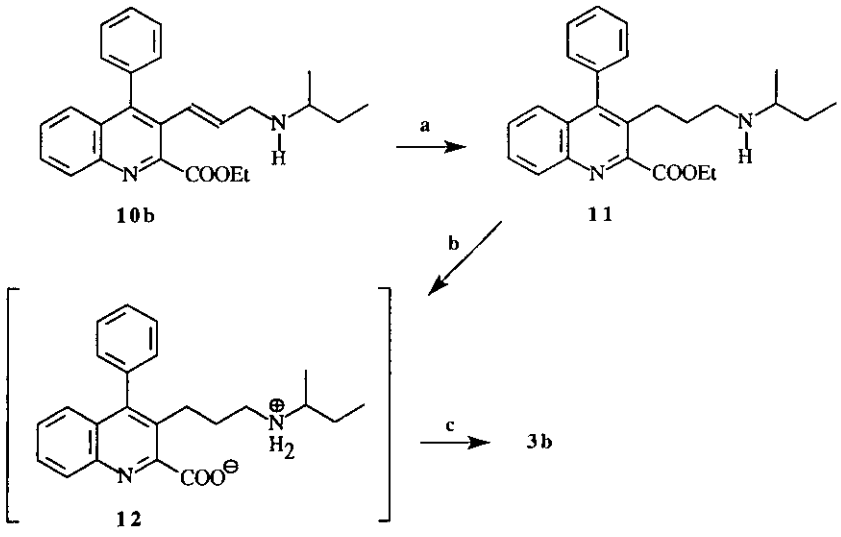


Reagents: a: PPh_3/C_6H_6; **b**: t-BuOK/C_6H_6; **c**: CH_3CHO/C_6H_6; **d**: NBS/CCl_4; **e**: R-NH_2/EtOH

f: H_2-Pd/C/EtOH; **g**: DMAP/PhMe.

Compound (4) was prepared, as we have reported,[4] and allowed to react with triphenylphosphine in refluxing benzene to give phosphonium salt (5). The methylene group of compound (5) proved to be acid enough to give the corresponding ylide (6) by reaction with potassium tert-butoxide at room temperature in 20-30 min. The ylide was then reacted with acetaldehyde in order to obtain the corresponding olefine (7). ^{1}H-Nmr spectra and GC-ms performed on the reaction mixture revealed along with the two geometric isomers of 7, the presence of compound (8), [4] which could be considered the hydrolysis product of the ylide. Due to its overcrowding the ylide probably prefers to behave as a base, and the hydrolysis could be an effect consequent to selfcondensation of the acetaldehyde promoted by the ylide itself. The most satisfactory yield was achieved when acetaldehyde was added to the refluxing ylide solution in benzene. Comparable results were obtained using tetrahydrofuran instead of benzene as solvent. However, some of the hydrolysis product was still present and the purification proved to be difficult; thus the reaction mixture was used for the next step after removal of the triphenylphosphine oxide by chromatography over alumina. After allylic bromination with N-bromosuccinimide, bromide (9) was purified by flash chromatography and characterized by its ^{1}H-nmr and mass spectra. [5] Compound (9) was then converted into allylamines (10a-c) by reaction with the suitable primary amine, [6] and the amines were subjected to mild catalytic hydrogenation and subsequent cyclization reaction to afford the title compounds. As for compounds (10a) and (10c), carrying out the cyclization reaction in boiling toluene in presence of 4-dimethylaminopyridine (DMAP) as catalyst, compounds (3a) and (3c) were obtained in satisfactory yields, while for compound (10b) the ring closure was proved to be slow even in refluxing xylene, perhaps because of steric hindrance near the nitrogen involved in the cyclization. After several attempts 3b was obtained in low yield and a large part of aminoester (11) (Scheme 2) was recovered unmodified; therefore we resolved to change the cyclization procedure.

Scheme 2



Reagents: a: H_2-Pd/C/EtOH; **b:** MeONa/EtOH; **c:** $SOCl_2/CH_2Cl_2$

First, 2-hydroxypyridine[7] was used instead of DMAP as catalyst in refluxing toluene and a significant yield improvement was observed. The most satisfactory results were obtained when 11 was treated with sodium methoxide in absolute ethanol and then with thionyl chloride in dichloromethane, in this way the cyclization probably proceeded through the amino acid intermediate (12), and 3b was obtained in 60% yield (Scheme 2).

EXPERIMENTAL

Melting points were determined in open capillaries on a Büchi 510 apparatus and are uncorrected. Microanalyses were carried out on a Perkin-Elmer 240C Elemental Analyzer. Merck silica gel 60, 70-230 or 230-400 mesh, was used for column normal or flash chromatography, respectively; Merck aluminumoxid 90 II-III, 70-230 mesh was used when indicated and Riedel-de Haen DC-Mikrokarten SI F 37341 were used as tlc. Ir spectra were recorded in nujol mulls with a Perkin-Elmer mod. 397 spectrophotometer. ^{1}H-Nmr spectra were recorded with a Bruker AC 200 spectrometer in the indicated solvents (TMS as internal standard); the values of chemical shifts are expressed in ppm and coupling costants (J) in Hz. Mass spectra (EI, 70 eV) were recorded on a VG 70-250S spectrometer. Ir, nmr spectra and elemental analyses were performed by Dipartimento Farmaco Chimico Tecnologico - Università di Siena. Mass spectra were performed by Centro di Analisi e Determinazioni Strutturali - Università di Siena.

[(2-Ethoxycarbonyl-4-phenylquinolin-3-yl)methyl]triphenylphosphonium bromide (5)

To a solution of 4[4] (1.7 g, 4.8 mmol) in anhydrous benzene (50 ml), triphenylphosphine (1.3 g, 5.0 mmol) was added and the resulting mixture was refluxed for 6 h. Then the precipitate was collected by filtration, washed with light petroleum ether and dried in vacuo over phosphorus pentoxide; 5 as white solid (2.6 g, 86%) was obtained melting at 218-220 °C. ^{1}H-Nmr ($CDCl_3$): 1.30 (t, J=7.0, 3H, CH_3), 4.16 (q, J=7.0, 2H, OCH_2), 5.49 (d, J=13.1, 2H, PCH_2), 7.18-7.84 (m, 23H, Ar-H), 8.21 (d, J=8.5, 1H, Ar-H).

E-3-(3-Bromo-1-propen-1-yl)-2-ethoxycarbonyl-4-phenylquinoline (9)

To a suspension of 5 (1.0 g, 1.58 mmol) in dry benzene (15 ml) under stirring at room temperature in argon atmosphere potassium t-butoxide (0.195 g, 1.74 mmol) was added and the resulting mixture was stirred at room temperature for 30 min. Then a solution of fresh distilled acetaldehyde (2.0 ml, 35.8 mmol) in dry benzene (5 ml) was added at 50-60 °C under stirring and the resulting mixture was kept to reflux for 6 h. The cooled reaction mixture was washed with water, dried over sodium sulfate and evaporated in vacuo and the residue was quickly passed through an alumina bed eluting with dichloromethane (0.46 g of a pale yellow oil). This oil was dissolved in carbon tetrachloride (30 ml) and N-bromosuccinimide (0.24 g, 0.135 mmol) and dibenzoyl peroxide (0.1 g, 0.41 mmol) were added and the resulting mixture was heated to reflux for 2 h. Then the succinimide was filtered-off, washed with a little amount of carbon tetrachloride and the filtrate was evaporated in vacuo. Purification of the residue by flash chromatography eluting with n-hexane-ethyl acetate (85:15) gave 9 (0.26 g, 42%) as pale yellow oil. ^{1}H-Nmr ($CDCl_3$): 1.44 (t, J=7.0, 3H, CH_3), 3.90 (d, J=7.5, 2H, CH_2Br), 4.52 (q, J=7.0, 2H, OCH_2), 5.82-5.98 (m, 1H, CH=C<u>H</u>-CH_2), 6.57 (d, J=16.0, 1H, C<u>H</u>=CH-CH_2), 7.24-7.28 (m, 2H, Ar-H), 7.43-7.80 (m, 6H, Ar-H), 8.20 (d, J=8.6, 1H, Ar-H). Ms Calcd for $C_{21}H_{17}NO_2Br$ $(M-H)^+$: 394.0443; found: 394.0439; Calcd for $C_{21}H_{18}NO_2$ $(M-Br)^+$: 316.1337; found:316.1328.

E-3-(3-Benzylamino-1-propen-1-yl)-2-ethoxycarbonyl-4-phenylquinoline hydrochloride (10a)

To a solution of 7 (0.24 g, 0.61 mmol) in ethanol (20 ml) benzylamine (0.4 ml, 3.66 mmol) was added and the resulting solution was refluxed for 30 min, then the volatile was removed in vacuo and 0.3 N hydrochloric acid, tetrahydrofuran and ether were added. The organic layer was discarted, while the aqueous solution was made alkaline with 3 N sodium hydroxide and extracted with dichloromethane. The organic extracts were dried over sodium sulfate and concentrated in vacuo; the residue was diluted with absolute ethanol and ethanolic 1 N hydrochloric acid (3 ml) was added. The solvent was removed in vacuo and the residue was dried by azeotropic distillation with toluene. Recrystallization from ethyl acetate gave 10a as a colourless crystalline powder (0.15 g, 54%). An analytical sample recrystallized from the same solvent melted at 186-187 °C. ^{1}H-Nmr ($CDCl_3$): 1.48 (t, J=7.2, 3H, CH_3), 3.32 (d, J=6.9, 2H, CH=CH-CH_2), 3.66 (s, 2H, CH_2Ph), 4.56 (q, J=7.2, 2H, OCH_2), 5.75-5.92 (m, 1H, CH=CH-CH_2), 6.67 (d, J=16.2, 1H, CH=CH-CH_2), 7.26-7.78 (m, 13H, Ar-H), 8.23 (d, J=8.4, 1H, Ar-H), 10.00 (br s, 2H, NH_2^+). Anal. Calcd for $C_{28}H_{27}N_2O_2Cl$: C, 73.27; H, 5.93; N, 6.10. Found: C, 73.03; H, 5.92; N, 6.09.

(±)-E-3-[3-(sec-Butylamino)-1-propen-1-yl]-2-ethoxycarbonyl-4-phenylquinoline hydrochloride (10b)

This compound was prepared by the same methodology described for compound (10a) from compound (9) and sec-butylamine (62% yield). An analytical sample recrystallized from ethyl methyl ketone melted at 201-202 °C. ^{1}H-Nmr ($CDCl_3$): 0.92 (t, J=7.4, 3H, CH_3-CH_2), 1.17 (d, J=6.5, 3H, CH_3-CH), 1.45-1.84 (m, 5H, CH_3 ester+CH_3-CH_2), 2.52-2.69 (m, 1H, CH), 3.42-3.66 (m, 2H, CH=CH-CH_2), 4.53 (q, J=7.2, 2H, OCH_2), 5.74-5.89 (m, 1H, CH=CH-CH_2), 6.76 (d, J=16.3, 1H, CH=CH-CH_2), 7.26-7.30 (m, 2H, Ar-H), 7.42-7.55 (m, 5H, Ar-H), 7.69-7.77 (m, 1H, Ar-H), 8.21 (d, J=8.6, 1H, Ar-H), 9.41 (br s, 2H, NH_2^+). Anal. Calcd for $C_{25}H_{29}N_2O_2Cl$: C, 70.66; H, 6.88; N, 6.59. Found: C, 70.65; H, 6.71; N, 6.54.

E-2-Ethoxycarbonyl-3-(3-methylamino-1-propen-1-yl)-4-phenylquinoline hydrochloride (10c)

This compound was prepared by the same methodology described for compound (10a) from compound (9) and 33% methylamine in ethanol (74% yield). An analytical sample recrystallized from ethyl acetate-ethanol melted at 241 °C (decomp.). ^{1}H-Nmr ($CDCl_3$): 1.47 (t, J=7.2, 3H, CH_3-CH_2O), 2.32 (br s, 3H, CH_3N), 3.52 (br s, 2H, CH=CH-CH_2), 4.54 (q, J=7.2, 2H, OCH_2), 5.66-5.81 (m, 1H, CH=CH-CH_2), 6.77 (d, J=16.1, 1H, CH=CH-CH_2), 7.25-7.28 (m, 2H, Ar-H), 7.41-7.56 (m, 5H, Ar-H), 7.67-7.78 (m, 1H, Ar-H), 8.22 (d, J=8.6, 1H, Ar-H), 9.57 (br s, 2H, NH_2^+). Anal. Calcd for $C_{22}H_{23}N_2O_2Cl$: C, 69.01; H, 6.06; N, 7.32. Found: C, 68.87; H, 6.12; N, 7.25.

4-Benzyl-11-phenyl-1,2,3,4-tetrahydro-5H-azepino[3,4-b]quinolin-5-one (3a)

A solution of compound (10a) as free base (0.166 g, 0.39 mmol) in ethanol (20 ml) with 10% palladium on activated carbon (0.20 g) was hydrogenated in Parr apparatus at 20 psi at room temperature for 30 min. Then the catalyst was removed by filtration through Celite and washed with hot ethanol. The filtrate was evaporated in vacuo and the residue was dissolved in toluene (20 ml), DMAP (0.1 g, 0.82 mmol) was added and the resulting mixture was heated to reflux in argon atmosphere for 48 h. Then the solvent was removed in vacuo and the residue was purified by column chromatography eluting with dichloromethane-ethyl acetate (8:2).

Recrystallization from cyclohexane-ethyl acetate gave 3a as white solid (0.065 g, 44%). An analytical sample melted at 200-201 °C. Ir: 1650 cm^{-1}. ^{1}H-Nmr ($CDCl_3$): 1.56-1.68 (m, 2H, CH_2), 2.66 (t, J=6.7, 2H, CH_2), 3.29 (t, J=6.2, 2H, CH_2), 4.88 (s, 2H, CH_2Ph), 7.20-7.74 (m, 13H, Ar-H), 8.39 (d, J=8.5, 1H, Ar-H). Anal. Calcd for $C_{26}H_{22}N_2O$: C, 82.51; H, 5.86; N, 7.40. Found: C, 82.67; H, 5.83; N, 7.44.

4-Methyl-11-phenyl-1,2,3,4-tetrahydro-5H-azepino[3,4-b]quinolin-5-one (3c)

Compound (10c) as free base (0.16 g, 0.46 mmol) was hydrogenated as described for compound (10a), then dissolved in toluene (50 ml) and DMAP (0.1 g, 0.82 mmol) was added. The resulting mixture was kept to reflux in argon atmosphere for 48 h, then the solvent was removed in vacuo and the residue was purified by column chromatography eluting with dichloromethane-ethyl acetate (8:2) to give 3c as colourless crystals (0.068 g, 49%). Recrystallization from cyclohexane-ethyl acetate gave an analytical sample melting at 217-218 °C. Ir: 1650 cm^{-1}. ^{1}H-Nmr ($CDCl_3$): 1.85-1.98 (m, 2H, CH_2), 2.71 (t, J=6.9, 2H, CH_2), 3.26 (s, 3H, CH_3), 3.32 (t, J=6.3, 2H, CH_2), 7.24-7.72 (m, 8H, Ar-H), 8.28 (d, J=8.5, 1H, Ar-H). Ms: m/z 302 (M^+, 100). Anal. Calcd for $C_{20}H_{18}N_2O$: C, 79.44; H, 6.00; N, 9.27. Found: C, 79.66; H, 6.15; N, 9.09.

(±)-3-[3-(sec-Butylamino)prop-1-yl]-2-ethoxycarbonyl-4-phenylquinoline (11)

A solution of compound (10b) as free base (0.45 g, 1.16 mmol) in ethanol (30 ml) with 10% palladium on activated carbon (0.50 g) was hydrogenated in Parr apparatus at 20 psi at room temperature for 40 min. Then the catalyst was removed by filtration through Celite and washed with hot ethanol. The filtrate was evaporated in vacuo and the residue was purified by column chromatography eluting with ethyl acetate-triethylamine (8:2) to give 11 (0.32 g, 71%) as pale yellow oil. ^{1}H-Nmr ($CDCl_3$): 0.80 (t, J=7.3, 3H, CH_3-CH_2), 0.91 (d, J=6.0, 3H, CH_3-CH), 1.12-1.69 (m, 8H, CH_3 ester+$2CH_2$+NH), 2.30-2.54 (m, 3H, CH_2+CH), 2.71-2.79 (m, 2H,CH_2), 4.54 (q, J=7.0, 2H, OCH_2), 7.24-7.70 (m, 8H, Ar-H), 8.17 (d, J=8.6, 1H, Ar-H). Ms: m/z Calcd for $C_{25}H_{30}N_2O_2$ (M^+): 390.2307. Found 390.2305.

(±)-4-(sec-Butyl)-11-phenyl-1,2,3,4-tetrahydro-5H-azepino[3,4-b]quinolin-5-one (3b)

To a solution of 11 (0.18 g, 0.46 mmol) in absolute ethanol (30 ml) a 30% sodium methoxide solution in methanol (2 ml, 10.8 mmol) was added and the resulting mixture was refluxed for 1 h. The cooled reaction mixture was then neutralized by addition of 1 N ethanolic hydrochloric acid and the solvent was removed in vacuo. The residue was diluted with dichloromethane (20 ml) and thionyl chloride (2 ml, 27.6 mmol) was added; after stirring at room temperature for 1 h, the volatile was distilled in vacuo, toluene (20 ml) was added and evaporated. The residue was partitioned between chloroform and sodium carbonate as saturated solution. The organic layer was washed with water, dried over sodium sulfate and concentrated in vacuo. Purification by column chromatography eluting with chloroform-ethyl acetate (8:2) gave 3b as oil wich crystallized on standing (0.095 g, 60%). An analytical sample recrystallized from cyclohexane-ethyl acetate melted at 165-166 °C. Ir: 1640 cm^{-1}. ^{1}H-Nmr ($CDCl_3$): 1.00 (t, J=7.4, 3H, CH_3-CH_2), 1.25 (d, J=6.6, 3H, CH_3-CH), 1.52-1.72 (m, 2H, CH_3-CH_2), 1.79-1.88 (m, 2H, CH_2), 2.74 (t, J=6.8, 2H, CH_2), 3.21 (t, J=6.4, 2H, CH_2), 4.87-4.97 (m, 1H, CH), 7.23-7.72 (m, 8H, Ar-H), 8.31 (d, J=8.7, 1H, Ar-H). Anal. Calcd for $C_{23}H_{24}N_2O$: C, 80.20; H, 7.02; N, 8.13. Found: C, 80.10; H, 6.92; N, 8.06.

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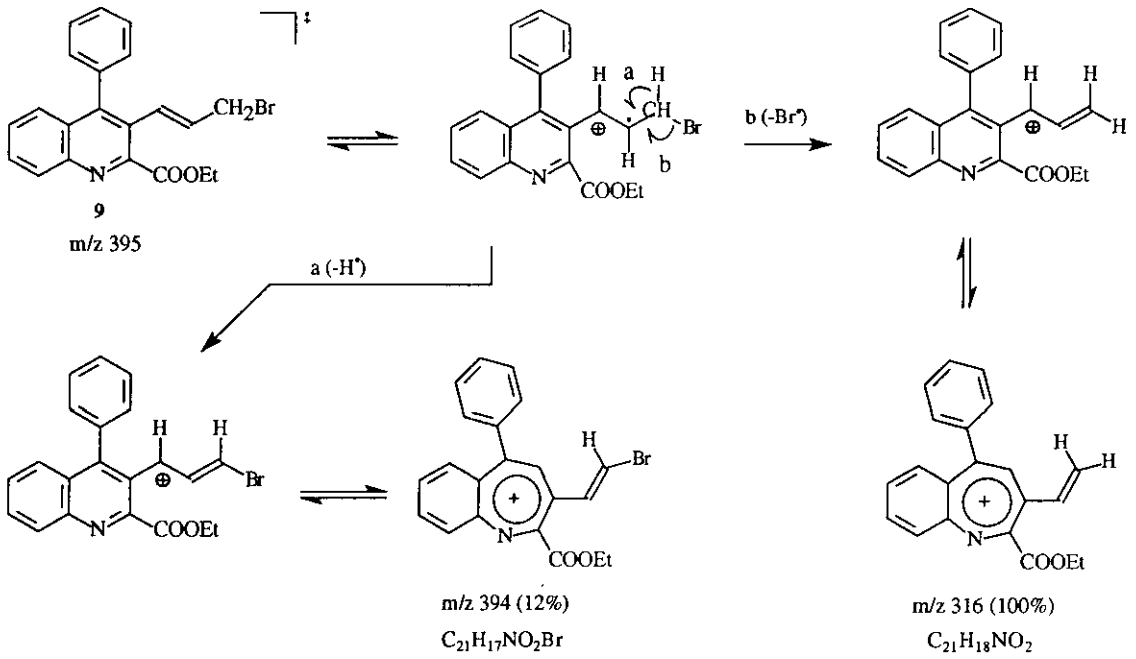
5. Mass spectrum of 9 performed in the usual conditions (EI, 70 eV) showed a very weak molecular ion and a more intense $(M-H)^+$ and $(M-Br)^+$ which constituted the most intense peak; the molecular ion could be better detected by reducing the electron energy, but it even showed only 30% of the $(M-H)^+$ intensity. The exact mass measure suggested for m/z 394 $(M-H)^+$ the molecular formula $C_{21}H_{17}NO_2Br$ and for m/z 316 $(M-Br)^+$ $C_{21}H_{18}NO_2$. These facts could be explained assuming the fragmentation pathway proposed in the scheme .



6. To avoid to tedious purification of the bromoolefine (9) by flash chromatography, the crude bromination product could be used in the subsequent amination step; thus pure amines (10a-c) were obtained in a more straightforward manner.
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