# Synthesis and Structural Study of Quinuclidine Spiro Derivatives

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The synthesis of quinuclidine-3-spiro-5'-oxazolidine-2',4'-dione, quinuclidine-3-spiro-5'-hydantoin, and some 3'-derivatives is described. Based on the data from $^1H$ and $^{13}C$-nmr spectra the structure of the above mentioned compounds is established. A relationship between second order effects in $^{13}C$-nmr spectra and H-C-C-H dihedral angles is deduced.

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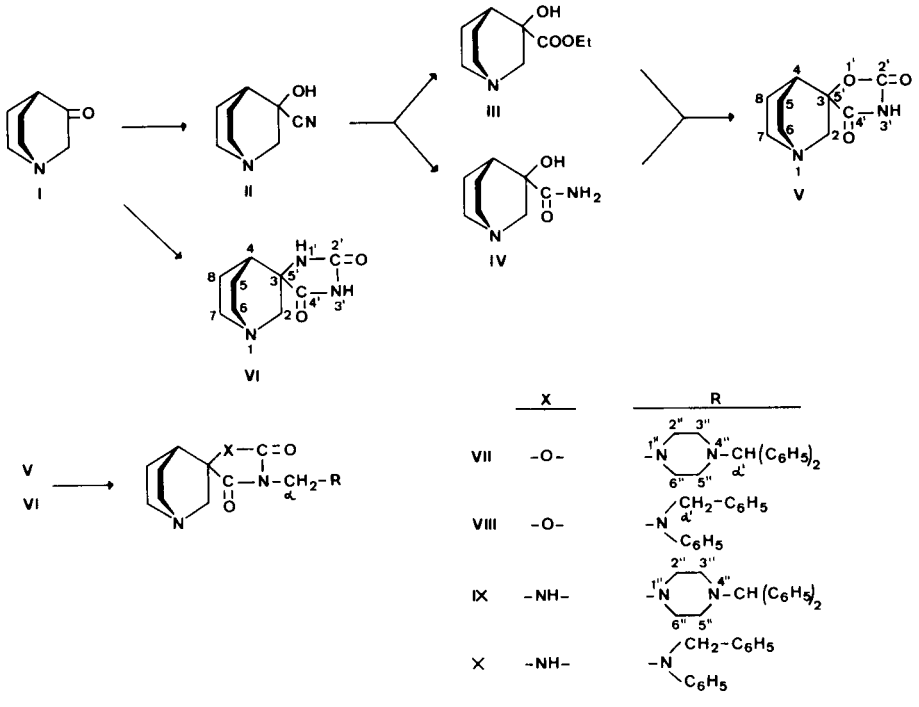
## Introduction.

A series of tropane and nortropane-3-spiro-5'-hydantoins previously synthesized by us (1), showed several pharmacological acativities (2-4). The structural relationship between the tropane and the quinuclidine system, the pharmacological properties reported in the case of the quinuclidine-3-spiro-5'-hydantoin (5), and the anticonvulsivant activity of oxazolidine-2',4'-diones prompted the synthesis of the new compound quinuclidine-3-spiro-5'-oxazolidine-2',4'-dione and the $^1H$-nmr and $^{13}C$-nmr study of these compounds with the objective of establishing a structure-activity relationship. We have synthesized and studied two new series of 3'-(4-benzhydrylpiperazinomethyl) and 3'-(*N*-benzyl-*N*-phenylaminomethyl) derivatives of the above mentioned compounds, keeping in mind the pharmacological properties of these substituents (6).

The pharmacological study of the new compounds is now being carried out.

## Scheme of the Synthesis.

The synthesis of quinuclidine-3-spiro-5'-oxazolidine-2',4'-dione, quinuclidine-3-spiro-5'-hydantoin and its 3'-(4-benzhydrylpiperazinomethyl) and 3'-(*N*-benzyl-*N*-phenylaminomethyl) derivatives is shown in Scheme 1. Quinuclidone (I) was transformed into the cyanohydrin II. The ethanolysis of II in acidic medium yielded the correspon-




Scheme 1

ding amidate, which was transformed by hydrolysis into the hydroxy ester III. Alternatively, the cyanohydrin II was hydrated in acidic medium and the hydroxy amide IV was obtained. Finally, condensation of III with urea, or condensation of IV with ethyl carbonate yielded the oxazolidine-2',4'-dione V.

The hydantoin VI was obtained from the quinuclidone I following the Bucherer-Bergs synthesis (7) by reaction of I, potassium cyanide and ammonium carbonate in aqueous ethanol.

Treatment of compounds V and VI with paraformaldehyde and a suitable amine yielded the corresponding 3'-derivatives VII, VIII, IX and X.

Results and Discussion.

IR Spectra.

The spectrum of compound VI in the solid state (potassium bromide) revealed a broad band in the 2500-2800 $cm^{-1}$ region, similar to the absorption formed in other azabicyclospirohydantoins (8); this absorption is explained by the existence of an intermolecular hydrogen bond which is formed between the weak acid N-3' H group and the basic quinuclidine nitrogen atom. The N-1' H stretching vibration originates a band in the 3300 $cm^{-1}$ region.

The carbonyl region shows a very strong band at 1730 $cm^{-1}$ with a shoulder at 1755 $cm^{-1}$; these bands are attributed to the asymmetrical and symmetrical modes of the pseudo-ring system formed between two molecules (N-1' H—O=C, C-2'). The band corresponding to C-4' C=O stretching vibration did not appear in the spectrum; this fact is explained by overlapping of the band corresponding to the C-2' C=O asymmetric stretching mode of the dimer. This interpretation is supported by studies carried

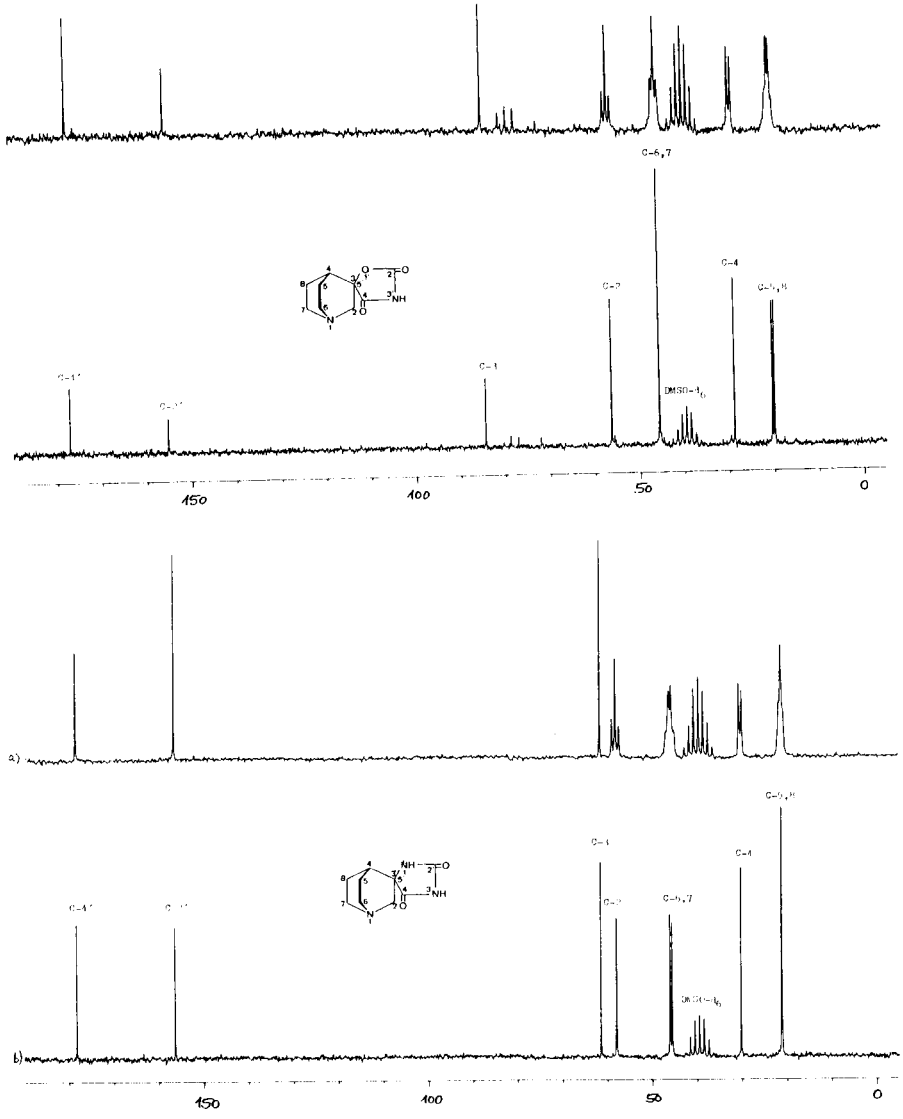



Figure 1

out on other azabicyclospirohydantoins (8,9). The spectrum of compound V in solid state (potassium bromide) showed a broad band in the 2000-2600 $cm^{-1}$ region which is explained in the same way as in the case of compound VI.

The ir spectra (potassium bromide) of compounds VII and IX showed two bands at 2750 and 2800 $cm^{-1}$ (Bohlmann's bands) which are due to the asymmetrical and symmetrical axial C-H stretching modes of the mechanical coupling, when two C-H axial bonds are in a *trans*-coplanar position with respect to the lone pair of an amine nitrogen atom (10-13). This fact implies that, as expected, in compounds VII and IX, the piperidine ring adopts a chair conformation, and the *N*-substituents are in equatorial positions.

NMR Spectra.

The $^1$H-nmr data are summarized in Table 1. It is noteworthy that, whereas the signal corresponding to 4-H in compound VI is a quintuplet, the same signal in compound V is a more complex multiplet. Presumably this fact is related to the non-equivalence of C-5,8 atoms in the $^{13}$C spectrum of compound V (Table 2).

In the spectra of compounds VII and IX, the symmetry of the well-separated multiplets corresponding to $H_{ax}$ ($\delta$ = 2.3-2.5) and $H_{eq}$ ($\delta$ = 2.5-2.7) of the piperazine ring shows that, in solution, the piperazine ring adopts a chair conformation and the groups attached to the nitrogen atoms are in equatorial positions. Furthermore, the aromatic proton resonance in the spectra of compounds VII and IX indicates a distinct conformational preference about the aryl-C in these compounds (14).

The $^{13}$C-nmr data are summarized in Table 2, in all cases noise decoupled and single frequencey off resonance decoupling spectra were obtained.

In the $^{13}$C SFORD spectra of compounds V and VI (Figure 1) can be seen the different resolution of the triplet due to C-2 with respect to the triplets corresponding to C-6,7 and to C-5,8. The less resolution (broadening) of the latter signals with respect to the former is explained in terms of virtual coupling. This is a situation where two sets of weakly coupled nuclei A and X are present, where one, A, is further strongly coupled to a species B. Even though X may not be coupled to B (as in this case) its resonance can still show second order characteristics (15,16). Up to this time, the second order effects in off-resonance proton-

Table 1

Chemical Shifts of Compounds V-X (a) ($\delta$, values; J, Hz values; TMS as the Internal Reference)

| Compound | Solvent | 2-H | 5(8)-H | 6(7)-H | 4-H | 1'-H | 3'-H | α-H | α'-H | CH-Ar |
|---|---|---|---|---|---|---|---|---|---|---|
| V (b) | $(CD_3)_2SO$ | 3.0 d<br>$^2J$ = 14<br>3.2 d | 1.3-2.2 m | 2.6-3.0 m | 2.18 m<br>$^3J$ = 3 | | 7.3 ws | | | |
| VI | $(CD_2)_2SO$ | 2.9 d<br>$^2J$ = 14<br>3.05 d | 1.1-1.5 m<br>1.9-2.4 m | 2.5-2.9 m | 1.78 q<br>$^3J$ = 3 | 7.4 s | | | | |
| VII | $CDCl_3$ | 3.0 d<br>$^2J$ = 15<br>3.3 d | 1.1-2.1 m | 2.7-3.0 m | 1.1-2.1 m | | | 4.5 s | 4.2 s | 7.1-7.4 m |
| IX | $CDCl_3$ | 2.9 d<br>$^2J$ = 16<br>3.3 d | 1.3-2.1 m | 2.7-3.1 m | 1.3-2.1 m | 8.3 s | | 4.5 s | 4.2 s | 7.1-7.5 m |
| X (c) | $CDCl_3$ | 2.8 d<br>$^2J$ = 14<br>3.2 d | 1.2-1.6 m<br>2.0-2.5 m | 2.8-3.0 m | 1.7 m | 8.1 s | | 5.2 s | 4.84 s | 7.2 s |

(a) The abbreviations, d (doublet), m (multiplet), q (quintuplet) and s (singlet) are used. (b) Spectra recorded at 310° K. (c) N-Ar protons give rise to a multiplet at 6.7-7.2.

Table 2

Carbon-13 Chemical Shifts of Compounds V and VI

| Compound | Solvent | C-2 | C-3 | C-4 | C-5,8 | C-6,7 | C-2' | C-4' |
|---|---|---|---|---|---|---|---|---|
| V | DMSO-$d_6$ | 56.22 | 84.38 | 28.77 | 20.32 | 45.55 | 155.20 | 177.13 |
| | 30% $CDCl_3$ | | | | 19.87 | | | |
| VI | DMSO-$d_6$ | 57.91 | 61.46 | 30.11 | 21.11 | 46.04 | 156.38 | 178.22 |
| | | | | | | 45.55 | | |

decoupled $^{13}$C-nmr spectra have been used to provide evidence that in the system $H_A$-$C_X$-$C_Y$-$H_B$, carbon atoms $C_X$ and $C_Y$ are adjacent to one another (17).

From the $^{13}$C spectra of the nearly rigid quinuclidine structure, we attempt to establish a semiquantitative relationship between the mentioned second-order effects and the $H_A$-$C_X$-$C_Y$-$H_B$ dihedral angles. In the case of C-6,7 and C-5,8, signals in SFORD $^{13}$C spectra of compounds V and VI, the off-resonance decoupling reduces the effective J $C_X$-$H_A$ coupling constant to the point where the vicinal coupling between the two pairs of vicinal protons becomes as large as the reduced J $C_X$-$H_A$; then, the carbon appears effectively coupled to HA and HB protons, and the corresponding triplet becomes unresolved. According to the above conclusion, when the dihedral angle $H_A$-$C_X$-$C_Y$-$H_B$ has a value of approximately 0° or 120°, the C-6,7 and C-5,8 triplets appears unresolved and, on the other hand, when the dihedral angle $H_A$-$C_X$-$C_Y$-$H_B$ has a value of $\cong$ 60° ($J_{H_a\text{-}H_b}$ = 3 Hz), the C-4 doublet appears resolved. Finally, it is important to note that the C-2 triplet appears quite resolved, this fact confirms the above conclusions.

By comparing the $^{13}$C spectra of compounds V and VI, there can be seen a shift of the signal corresponding to the oxazolidine-2',4'-dione spiro atom of 22.92 ppm to lower field with respect to the signal corresponding to the hydantoin spiro atom; this is due to the greater $\sigma$-effect exerted by the oxygen with respect to nitrogen atom.

## EXPERIMENTAL

All melting points were taken in open capillary tubes and are uncorrected. Infrared spectra were determined using a Perkin-Elmer 577 spectrophotometer. The $^1$H-nmr spectra have been recorded using a Varian EM 390 operating at 90 MHz and a Bruker WP 80 SY spectrometer operating at 80 MHz. The $^{13}$C-nmr spectra were determined on a Bruker WP 80 SY spectrometer operating at 20 MHz. All samples were contained in precision ground 5 mm O. D. tubes. On the average, a 2.5 $\mu$s pulse, corresponding to an approximate tilt angle of 45°, was employed. Noise decoupled and single frequency off resonance decoupled spectra have been obtained with 1300 and 3400 scans in the case of compound V, and with 1000 and 4000 for compound VI respectively. The spectral width was 5000 Hz; concentrations *c.a.* 80 mg/0.5 ml and 16 K memory points. The mass spectra were determined on a Hitachi Perkin-Elmer RMU-6M spectrometer. The elemental analysis were made in a Carlo Erba Elemental Analyzer model 1104 equipped with a C. S. I. digital integrator model C SI 38.

Quinuclidone.

This compound was obtained from Aldrich Chemical Company.

3-Hydroxyquinuclidine-3-carbonitrile (II).

A solution of potassium cyanide (0.093 mole) in water (19.5 ml) was added dropwise to a solution of quinuclidine hydrochloride (0.093 mole) in water (19.5 ml), externally cooled with ice and magnetically stirred for 15 minutes; then the stirring was maintained for 3 hours. The precipitated solid was filtered under reduced pressure and washed with water, mp 150° (98%); ir (potassium bromide): 3300-3600 (O-H), 2220 (C≡N) cm$^{-1}$.

*Anal.* Calcd. for $C_8H_{12}N_2O$: C, 63.13; H, 7.94; N, 18.40. Found: C, 63.36; H, 7.98; N, 18.25.

3-Hydroxyquinuclidine-3-carboxamide (IV).

Compound II (0.13 mole) was added gradually to concentrated sulfuric acid (40 ml) externally cooled. The mixture was maintained at room temperature for 48 hours, then was added over powdered ice (15 g). The resulting solution was neutralized with barium carbonate and the precipitate of barium sulfate was separated. The solution was concentrated under reduced pressure and the precipitated solid recrystallized from ethanol, mp 170° (58%); ir (potassium bromide): 3420 (O-H), 3260 and 3170 ($NH_2$), 1655 (C=O), 1570 ($NH_2$) cm$^{-1}$.

*Anal.* Calcd. for $C_8H_{14}N_2O_2$: C, 56.45; H, 8.29; N, 16.45. Found: C, 56.22; H, 8.12; N, 16.30.

Ethyl 3-Hydroxyquinuclidine-3-carboxylate (III).

Anhydrous hydrogen chloride was bubbled into a solution of II (0.04 mole) in ethanol (150 ml) until saturation with external cooling and magnetic stirring. The mixture was maintained at 0° for 48 hours. The precipitated solid was filtered off. To the mother liquor was added diethyl ether (v/v) and the resulting solution was maintained at 0° for 24 hours. The precipitated solid was filtered off. The solid precipitates (10 g) were identified by ir as the corresponding imidate, which was dissolved in aqueous hydrochloric acid (10%), the solution was stirred for 30 minutes, neutralized with sodium carbonate and treated with three portions of diethyl ether (25 ml). The ethereal solution was dried with anhydrous sodium sulfate, filtered and the solvent evaporated; the white precipitate was recrystallized from ethanol, mp 110° (55%); ir (potassium bromide): 3420 (O-H), 1720 (C=O) cm$^{-1}$.

*Anal.* Calcd. for $C_{10}H_{17}O_3N$: C, 60.28; H, 8.59; N, 7.03. Found: C, 60.46; H, 8.80; N, 7.24.

Quinuclidine-3-spiro-5'-oxazolidine-2',4'-dione (V).

Method A.

To a solution of sodium methoxide [sodium (0.52 g) in methanol (10.5 ml)], was added another solution of IV (0.023 mole) and diethyl carbonate (4.3 ml) in methanol (50 ml). The resulting mixture was refluxed at 80° for 48 hours. The solvent was evaporated under reduced pressure, the residue was taken up with cold water (15 ml) and neutralized with aqueous hydrochloric acid (2*N*). The solution was concentrated under reduced pressure to half volume. The solid precipitate was filtered and recrystallized from ethanol, mp 185° (76%); ir (potassium bromide): 1750 and 1715 (C=O) cm$^{-1}$. The mass spectrum of the product had a molecular ion peak at m/e 197 with abundant fragment peaks at m/e 196, 125, 98, 97, 96, 95, 82, 81, 80, 70, 69, 68, 67, 55, 54 and 44.

*Anal.* Calcd. for $C_9H_{12}N_2O_3$: C, 50.56; H, 6.56; N, 13.05. Found: C, 50.34; H, 6.36; N, 12.84.

Method B.

A solution of III (0.005 mole) sodium (0.1 g) and urea (0.005 mole) in ethanol (9 ml) was refluxed for 48 hours, then the solution was concentrated *in vacuo* to dryness. The residue was dissolved in cold water (3 ml) and neutralized with aqueous hydrochloric acid (2*N*) to *p*H = 6.5. The resulting solution was maintained at 0° and the solid precipitate was recrystallized from ethanol, mp 186° (30%). Ir and mass spectral data are the same as described above.

*Anal.* Calcd. for $C_9H_{12}N_2O_3$: C, 50.56; H, 6.56; N, 13.05. Found: C, 50.40; H, 6.45; N, 12.86.

Quinuclidine-3-spiro-5'-hydantoin (VI).

To a solution of potassium cyanide (0.09 mole) and ammonium carbonate (17.25 g) in water (75 ml) was added another solution of quinuclidone hydrochloride (0.06 mole) in ethanol (25 ml). The resulting solution was heated in a sealed flask at 60° for 24 hours. After cooling the solution was concentrated under reduced pressure until half of the initial volume. The solid precipitate was filtered under reduced pressure and recyrstallized from ethanol, mp 280° (88%). The mass spectrum of the product had a molecular ion-peak at m/e 196 with abundant fragment peaks at m/e 195, 152, 138, 123, 96, 84, 83, 82, 81, 70, 69, 68, 67, 58, 57, 56, 55, 54, 53 and 44.

*Anal.* Calcd. for $C_9H_{13}N_3O_2$: C, 55.37; H, 6.71; N, 21.52. Found: C, 55.15; H, 6.67; N, 21.26.

Preparation of Compounds VII, VIII, IX and X.

A solution of V or VI (0.01 mole), 40% aqueous formaldehyde (1 ml) and a suitable amine (0.01 mole) (18,19) in ethanol (40 ml) was refluxed with magnetic stirring for 2 hours, then the solution was concentrated under reduced pressure until one third of the initial volume. The solid precipitate was recrystallized. In the case of compounds VIII and IX, the reduction mixture was concentrated under reduced pressure until dryness and the residue recrystallized.

3'-[(4-Benzhydrylpiperazino)methyl]quinuclidine-3-spiro-5'-oxazolidine-2',4'-dione (VII).

This compound was obtained in a yield of 57% mp 115° (from methanol); ir (potassium bromide): 2800 and 2750 (C-$H_{ax}$), 1800 and 1725 (C=O) $cm^{-1}$. The mass spectrum of the product had a molecular ion-peak at m/e 461 with abundant fragment peaks at m/e 383, 265, 264, 251, 209, 196, 168, 167, 166, 165, 152, 98, 97, 96, 91, 89, 77, 57, 56, 55 and 44.

*Anal.* Calcd. for $C_{27}H_{32}N_4O_3$: C, 70.40; H, 7.00; N, 12.16. Found: C, 70.18; H, 60.90; N, 12.05.

3'-(*N*-Benzyl-*N*-phenylaminomethyl)quinuclidine-3-spiro-5'-oxazolidine-2',4'-dione (VIII).

The product was an oil (methanol) obtained in a yield of 52%; ir (film): 1805 and 1725 (C=O) $cm^{-1}$. The mass spectrum of the product had a molecular ion peak at m/e 392 with abundant fragment peaks at m/e 391, 243, 242, 228, 197, 196, 195, 194, 184, 183, 182, 181, 180, 120, 106, 105, 104, 97, 93, 92, 91, 90, 79, 78, 77, 65, 64, 63, 62, 59, 54, 52, 51 and 50.

*Anal.* Calcd. for $C_{23}H_{26}N_3O_3$: C, 70.38; H, 6.67; N, 10.70. Found: C, 70.10; H, 6.32; N, 10.40.

3'-[(-4-Benzhydrylpiperazino)methyl]quinuclidine-3-spiro-5'-hydantoin (IX).

This compound was obtained in a yield of 53% mp 140° (from ethanol); ir (potassium bromide): 3220 (NH), 2800 and 2760 (C-$H_{ax}$), 1760 and 1705 (C=O) $cm^{-1}$. The mass spectrum of the product had abundant fragment peaks at m/e 265, 264, 262, 167, 166, 152, 150, 98, 97, 96, 95, 83, 82, 56, 55, 54 and 44.

*Anal.* Calcd. for $C_{27}H_{33}N_5O_2$: C, 70.56; H, 7.23; N, 15.23. Found: C, 70.30; H, 7.50; N, 15.00.

3'-(*N*-Benzyl-*N*-phenylaminomethyl)quinuclidine-3-spiro-5'-hydantoin (X).

This compound was obtained in a yield of 65%, mp 175° (from methanol); ir (potassium bromide): 2860-2500 (NH), 1750 and 1700 (C=O) $cm^{-1}$. The mass spectrum of the product had a molecular ion peak at m/e 391 with abundant fragment peaks at m/e 197, 196, 195, 194, 182, 104, 92, 91, 77, 70, 68, 67, 65, 51 and 44.

*Anal.* Calcd. for $C_{23}H_{27}N_4O_2$: C, 70.56; H, 6.95; N, 14.31. Found: C, 70.30; H, 7.07; N, 14.20.

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