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Structural Characterization of (±)-3-Aryl-1-azabicyclo[2.2.2]octan-3-ols by Two-Dimensional NMR Spectroscopy and X-Ray Crystallography. I.

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A series of (±)-3-aryl-1-azabicyclo[2.2.2]octan-3-ols were synthesized and studied by ^{1}H, ^{13}C and 2D NMR spectroscopy, and the crystal structure of (±)-3-(4-methylphenyl)-1-azabicyclo[2.2.2]octan-3-ol was determined by X-ray diffraction. The combined use of COSY, NOESY and ^{1}H-^{13}C correlation spectra of these compounds helped in the unambiguous and complete assignments of the bicyclic carbon and proton spin system. This study allows the establishment of the proton magnetic parameters for the quinuclidine moiety. Standard values of ^{1}H–^{1}H coupling constants are proposed in order to analyse more complex quinuclidine derivatives.

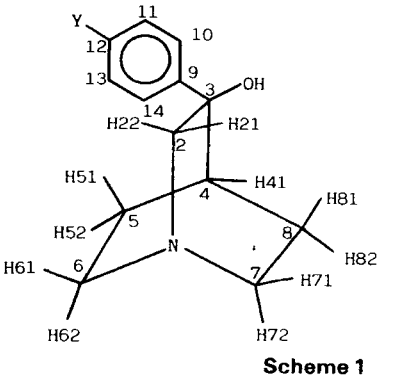
KEY WORDS 3-Aryl-1-azabicyclo[2.2.2]octan-3-ols 2D NMR (COSY, NOESY and ^{1}H-^{13}C correlated spectroscopy) ^{1}H–^{1}H coupling constants in quinuclidine derivatives

INTRODUCTION

There has been considerable recent interest in the development of pharmacologically active molecules that display enhanced receptor selectivity and more narrow spectra of pharmacological actions. One approach towards the development of more receptor-selective ligands is the incorporation of conformational restrictions. Conformationally restricted analogues afford the advantage of being more amenable to conformational analysis because they are less subject than more flexible molecules to conformational averaging, and their solution conformations are more realistically extrapolated to the active binding conformation. Thus, different 1-azabicyclo[2.2.2]octane (quinuclidine) derivatives have been described as potent agonists and antagonists of muscarinic receptors[1–4].

In connection with our interest in the preparation and pharmacological screening of monoaza- and diazabicyclo derivatives[5–7] we have focused our attention on the role of an aryl ring in the 3-position of 1-azabicyclo[2.2.2]octan-3-ol. We report here the spectrocopic study of (±)-3-aryl-1-azabicyclo[2.2.2]octan-3-ols **1–4** (Scheme 1) as well as the crystal structure of (±)-3-(4-methylphenyl)-1-azabicyclo[2.2.2]octan-3-ol (**1**). Few data have been found in the literature for **1**[8] and (±)-3-(4-methoxyphenyl)-1-azabicyclo[2.2.2]octan-3-ol (**2**)[9], and (±)-3-(4-chlorophenyl)-1-azabicyclo[2.2.2]octan-3-ol (**3**) has only been reported in connection with some pharmacological tests[10]. (±)3-(4-Fluorophenyl)-1-azabicyclo[2.2.2]octan-3-ol (**4**), to our knowledge, has not been previously described.

Due to the complexity of the quinuclidine system, its proton magnetic parameters have often not been reported in sufficient detail.[2,3,11] In this paper, compounds **1–4** have been studied in depth by ^{1}H- and ^{13}C-NMR. The assignment of all bicyclic proton and carbon resonances has been achieved through the application of two-dimensional NMR techniques.[12–17] In particular, homonuclear correlated spectroscopy (COSY-45),[14,15] nuclear Overhauser enhancement spectrocopy (NOESY)[16,17] and heteronuclear ^{1}H-^{13}C correlated spectroscopy (XHCORRD)[14,18] were used. The observed ^{1}H–^{1}H coupling constants are proposed as standard values in order to carry out the analysis of more complex quinuclidine derivatives.



1, Y = CH_3
2, Y = OCH_3
3, Y = Cl
4, Y = F

Scheme 1

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EXPERIMENTAL

The melting points were uncorrected. The IR spectra were recorded on KBr pellets on a Perkin-Elmer 883 spectrophotometer.

Synthesis

3-Aryl-3-quinuclidinols **1**, **2** and **4** were prepared following standard procedures by the addition of 3-quinuclidone (16 mmol) to the respective arylmagnesium bromide in diethyl ether (obtained from magnesium (35 mmol) and the aryl bromide (33 mmol)) under nitrogen at 0 °C. Once the addition was completed the mixture was allowed to attain room temperature and refluxed for 6 h. The mixture was hydrolysed with a saturated solution of NH_4Cl and extracted with dichloromethane (except for **4** which was isolated following the procedure described previously[9]). The organic layer was dried ($MgSO_4$), and after removal of the solvent the alcohols were purified by fractional recrystallization from acetone.

(±)—3-(4-Methylphenyl)-1-azabicyclo[2.2.2]octan-3-ol (**1**) (52% yield): m.p., 142–4 °C. (Found: C, 77.52; H, 8.49; N, 6.20. Calc. for $C_{14}H_{19}NO$: C, 77.38; H, 8.81; N, 6.45). IR, $\nu_{max} = 3050\ cm^{-1}$.

(±)—3-(4-Methoxyphenyl)-1-azabicyclo[2.2.2]octan-3-ol (**2**) (43% yield): m.p, 145–6 °C. (Found: C, 72.38; H, 8.55; N, 6.00. Calc. for $C_{14}H_{19}NO_2$: C, 72.07; H, 8.20; N, 6.00). IR, $\nu_{max} = 3090\ cm^{-1}$.

(±)—3-(4-Fluorophenyl)-1-azabicyclo[2.2.2]octan-3-ol (**4**) (33% yield): m.p., 133–4 °C. (Found: C, 70.22; H, 7.56; N, 6.46. Calc. for $C_{13}H_{16}FNO$: C, 70.58; H, 7.24; N, 6.33). IR, $\nu_{max} = 3080\ cm^{-1}$.

(±)—3-(4-Chlorophenyl)-1-azabicyclo[2.2.2]octan-3-ol (**3**) was synthesized by the procedure described by Langbein *et al.*[19] for related systems, using *p*-chlorophenyllithium as the organometallic reagent. The work-up described above was applied for its isolation and purification. (38% yield): m.p., 181–2 °C. (Found: C, 65.68; H, 7.38; N, 5.69. Calc. for $C_{13}H_{16}ClNO$: C, 65.68; H, 6.78; N, 5.89). IR, $\nu_{max} = 3045\ cm^{-1}$.

NMR Spectra

All measurements were carried out at 293 °K using ca. 0.25 M solutions in $CDCl_3$ with TMS as the internal reference.

The ^1H and ^{13}C NMR spectra were recorded on a Varian UNITY-300FT spectrometer (299.949 MHz for ^1H and 75.429 MHz for ^{13}C). The ^1H NMR spectral parameters included sweep widths of 4000 Hz in 24 K memory size; ^1H 45° pulse width 6.9 μs; acquisition time 3 s over 64 transients. Resolution enhancement using LB = −0.8, GF = 0.6 and GFS = 0.2 was followed by zero filling into 64 K memory space prior to Fourier transformation. The digital resolution obtained was 0.122 Hz per point. The double resonance (DR) experiments involved the use of conventional irradiation and decoupler powers over the range 15–10 L.

The ^{13}C NMR recording conditions were as follows: spectral width 16501.7 Hz; ^{13}C 45° pulse width 4.0 μs; acquisition time 1 s and relaxation delay 1 s in 64 K memory size. DEPT experiments[14] were carried out using a ^{13}C 90° pulse width (8.0 μs), ^1H 90° decoupler pulse width 13 μs, relaxation delay 2 s and variable pulse θ 135°, providing information about the number of C-attached protons.

The 2D homonuclear ^1H–^1H COSY-45[14,15] and NOESY[16,17] experiments were performed for **1** at 500 MHz on a Bruker AM-500 FT NMR spectrometer, using standard pulse sequences, with sweep widths of 3472 Hz in the F2 domain (1731 Hz in F1), memory size in F2 of 2 K and in F1 of 1 K (zero filling in F1) over 300 experiments. A sine bell window function was applied in both domains. The 90° ^1H pulse width was 11.9 μs. A relaxation delay of 1.9 s was used for the COSY experiment and each experiment involved eight transients with two dummy scans. The NOESY experiment was carried out using a relaxation time of 1.6 s, a mixing time of 0.7 s and a random variation of 15% in mixing time to reduce *J*-responses.[17] In this latter case, a total of sixteen transients (with two dummy scans) were collected for each experiment.

Heteronuclear ^1H–^{13}C correlation experiments were performed for **1** on a Bruker AM-300FT NMR spectrometer using the XHCORRD.AU microprogram.[18] The ^1H 90° pulse width was 9.6 μs and the ^{13}C 90° pulse width was 3.7 μs. Proton spin decoupling was achieved using a decoupler power of 15 H. The experiment was carried out using a sweep width of 11111 Hz in the F2 domain (^{13}C) and 2200 Hz in the F1 domain (^1H), a memory size in F2 of 2 K and in F1 of 1 K, over 128 experiments, each involving 32 transients (with two dummy scans). A relaxation delay of 2 s was used and the fixed delay times were calculated from a compromise value of $^1J(CH) = 140$ Hz. A sine bell window function was applied in both domains, before zero filling in F1, for the 2D Fourier transformation.

The agreement between the observed spectra and the parameters deduced from analysis with the LAOCOON III program[20] was verified by simulation of the calculated spectra.

X-ray diffraction

The main crystallographic data and the structure determination conditions for compound **1** are given in Table 1.

RESULTS AND DISCUSSION

X-ray crystal structure analysis of 1

The ORTEP view of the molecule, together with the atomic labelling, is shown in Fig. 1. The atomic parameters are given in Table 2 and some selected bond

Table 1. Experimental Data and Structure Refinement Procedures for Compound 1

Crystal data	
Formula	$C_{14}H_{19}NO$
Crystal size (mm)	0.40 × 0.40 × 0.50
Symmetry	Monoclinic, CC
Unit cell determination	Least-squares fit from 25 reflections ($10 < \theta < 30°$)
Unit cell dimensions	12.505 (5), 11.268 (2), 10.612 (2) Å 90.0, 125.80 (2), 90.0
Packing: V(Å^3), Z	1212.8 (6), 4
Dc(g. cm^{-3}), M, F(000)	1.1902, 217.310, 472
μ(cm^{-1})	0.693
Experimental data	
Technique	Four circle diffractometer: Enraf-nonius, CAD-4 Bisecting geometry Graphite oriented monochromator: Mo Kα $\omega/2\theta$ scan
Scanning range for θ	$2 < \theta < 30°$
Number of reflections:	
Measured	1758
Observed	1002 ($I > 3\sigma(I)$ criterion)
Absorption	No correction applied
Solution and refinement	
Solution	Direct methods
Refinement	Mixed, non-hydrogen atoms anisotropic, hydrogen atoms isotropic
Variables	219
H atoms	Differential Fourier synthesis and geometric calculations
W-scheme	Empirical, so as to give no trends in $\langle w\Delta 2F \rangle$ vs. $\langle \|Fo\| \rangle$ and $\langle \sin\theta/\lambda \rangle$ [21]
Final shift/error	0.05
Final R and Rw	0.050, 0.055
Final ΔF peaks	0.17 e Å^{-3}
Computer and programs	Vax 11/750, Multan80[22], X-ray 76[23] Parts[24]
Scattering factors	International Tables for X-Ray Crystallography[25]
Anomalous dispersion	International Tables for X-Ray Crystallography[25]

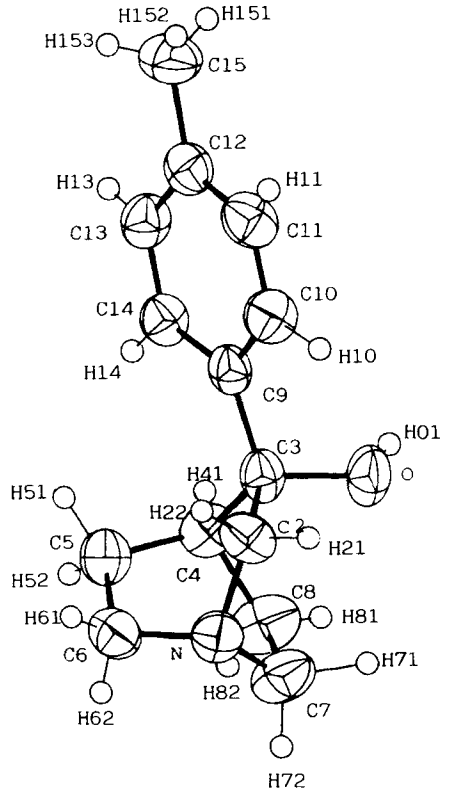

Figure 1. ORTEP view of **1** and atomic labelling.

Table 2. Atomic coordinates and thermal parameters for non-hydrogen atoms of 1[a,b]

Atom	X/A	Y/B	Z/C	Ueq[c]
O	0.4934 (5)	0.3074 (3)	0.8311 (6)	63 (3)
N	0.2264 (6)	0.1505 (4)	0.6203 (7)	53 (3)
C3	0.4704 (0)	0.1885 (4)	0.7731 (0)	46 (3)
C2	0.3337 (6)	0.1927 (5)	0.6137 (7)	52 (3)
C7	0.2384 (7)	0.2068 (7)	0.7532 (8)	70 (4)
C8	0.3633 (8)	0.1628 (8)	0.9078 (8)	74 (4)
C4	0.4532 (7)	0.1031 (5)	0.8735 (7)	52 (3)
C5	0.3850 (7)	−0.0093 (5)	0.7812 (8)	58 (3)
C6	0.2430 (6)	0.0214 (5)	0.6463 (9)	61 (4)
C9	0.5789 (6)	0.1555 (4)	0.7554 (7)	43 (2)
C10	0.5955 (7)	0.2234 (5)	0.6585 (8)	55 (3)
C11	0.6972 (7)	0.2031 (5)	0.6463 (8)	60 (4)
C12	0.7911 (6)	0.1172 (4)	0.7329 (7)	50 (3)
C13	0.7747 (6)	0.0476 (4)	0.8275 (7)	53 (3)
C14	0.6709 (6)	0.0644 (4)	0.8386 (7)	49 (3)
C15	0.9079 (8)	0.1001 (7)	0.7273 (9)	69 (5)

[a] Error standard deviations (e.s.d. values) are given in parentheses.
[b] For atomic labelling, see Fig. 1.
[c] Ueq = 1/3 ΣiΣj[Uij.ai*.aj*.ai.aj.cos(ai,aj)].10**3.

lengths, bond and torsion angles are given in Tables 3 and 4.

The quinuclidine moiety has a skew conformation and the molecule is seen in Fig. 1 along the N–C_5 (threefold) axis; the C_2–N ... C_4–C_3 = 10.9°, C_7–N ... C_4–C_8 = 9.4° and C_6–N ... C_4–C_5 = 9.4° torsion values are twice those found in some monosubstituted quinuclidine compounds[26] but similar to those of disubstituted compounds,[27] although in this case both substituents are in the same position. These data emphasize the determining influence of the substituents on the torsion angles with respect to the quinuclidine molecule, which seems to present no such distortion.[28] All bond distances and valence angles correspond to the expected values. Consequently, with the above considerations, the three condensed rings have a boat-twist conformation and the bicyclic atoms with less mobility correspond to bridgehead atoms (N and C_4) and a disubstituted carbon C_3.

Fig. 2 shows a view of the molecular packing in the unit cell. As can be seen, the structure is formed by chains oriented along the *a* axis and linked by hydrogen bonds between the hydroxyl oxygen and the nitrogen atoms of the azabicycle: O ... N (X + 1/2, Y + 1/2, Z + 1/2) = 2.77, H–O = 0.84 and H01 ... N = 1.92 Å and O–H01 ... N = 177°.

The N–O distance is 3.25 (5) Å, similar to that found for 3-quinuclidinol (≈3.5 Å).[29] Thus, it might be assumed that the 3-aryl-3-quinuclidinols **1–4** fit the simple distance geometry pharmacophore, constraints established previously for the acethylcholine receptor.[30]

Table 3. Bond lengths (Å) and angles (°) in 1[a,b]

Bond	Length (Å)	Bond	Length (Å)
	Bond Lengths		
O–C3	1.432 (6)	N–C2	1.46 (1)
N–C7	1.47 (1)	N–C6	1.472 (7)
C3–C2	1.550 (5)	C3–C4	1.541 (9)
C3–C9	1.520 (9)	C7–C8	1.542 (9)
C8–C4	1.52 (1)	C4–C5	1.521 (7)
C5–C6	1.532 (8)	C9–C10	1.39 (1)
C9–C14	1.403 (7)	C10–C11	1.37 (1)
C11–C12	1.377 (8)	C12–C13	1.38 (1)
C12–C15	1.51 (1)	C13–C14	1.38 (1)
	Bond Angles (°)		
Angle	Value (°)	Angle	Value (°)
C7–N–C6	108.8 (6)	C2–N–C6	107.3 (6)
C2–N–C7	108.8 (5)	O–C3–C9	108.2 (4)
O–C3–C4	111.2 (3)	O–C3–C2	104.9 (3)
C4–C3–C9	115.4 (3)	C2–C3–C9	111.5 (3)
C2–C3–C4	105.3 (4)	N–C2–C3	113.2 (5)
N–C7–C8	110.7 (7)	C7–C8–C4	108.5 (6)
C3–C4–C8	108.0 (5)	C8–C4–C5	107.9 (7)
C3–C4–C5	109.1 (5)	C4–C5–C6	108.7 (5)
N–C6–C5	110.9 (5)	C3–C9–C14	124.3 (6)
C3–C9–C10	119.1 (5)	C10–C9–C14	116.4 (7)
C9–C10–C11	121.7 (5)	C10–C11–C12	122.1 (7)
C11–C12–C15	122.1 (6)	C11–C12–C13	116.9 (7)
C13–C12–C15	121.0 (6)	C12–C13–C14	122.0 (5)
C9–C14–C13	120.8 (5)		

[a] E.s.d. values are given in parentheses.
[b] For atomic labelling, see Fig. 1.

Table 4. Torsion angles (°) in 1[a,b]

Angle	Value (°)
O–C3–C9–C10	−58.9 (7)
C4–C3–C9–C10	175.8 (6)
C2–C3–C9–C10	55.8 (7)
C4–C3–C2–N	18.1 (6)
C4–C5–C6–N	15.7 (8)
O–C3–C9–C14	116.8 (6)
C4–C3–C9–C14	−8.4 (8)
C2–C3–C9–C14	−128.4 (6)
N–C7–C8–C4	15.7 (9)
H41–C4–C5–H51	−64 (6)
H41–C4–C5–H52	50 (6)
H81–C8–C4–H41	40 (7)
H82–C8–C4–H41	−75 (7)
H51–C5–C6–H61	13 (5)
H51–C5–C6–H62	137 (4)
H52–C5–C6–H61	−101 (6)
H52–C5–C6–H62	22 (5)
H71–C7–C8–H81	24 (7)
H71–C7–C8–H82	137 (6)
H72–C7–C8–H81	−96 (7)
H72–C7–C8–H82	17 (6)

[a] E.s.d. values are given in parentheses.
[b] For atomic labelling, see Fig. 1.

On the other hand, the distance from the nitrogen to the centre of the aryl moiety is 5.09 (3) Å, near to the distance from the protonated nitrogen to the centre of the nearest phenyl ring in the first M1 selective muscarinic receptor antagonist (pirenzepine)[31] in the energetically favourable conformation (6–7 Å).[32]

Spectral analysis

At 300 MHz in $CDCl_3$ solutions the ^1H NMR spectra of 3-aryl-3-quinuclidinols **1–4** are very similar, exhibiting the bicyclic system proton resonances contained in the region between 1.30 and 3.50 ppm. Thus, for **1** (Fig. 3) the respective multiplets are due to one proton, except for those centred at ca. 2.88, 2.58 and 1.40 which correspond to two protons. The signals due to C-2 and the bridgehead, H-41, protons are well differentiated at 3.29, 2.88 and 2.07 ppm, respectively, while the other proton resonances exhibit high complexity. The H-41 signal appears as a quintet and the H-21 and H-22 signals as doublets of doublets because of the long-range (W) couplings with H-62 and H-72, respectively (Scheme 1).

The 2D NOESY[16,17] spectrum of **1** was utilized in coordination with the COSY[14,15] spectrum, recorded at 500 MHz in $CDCl_3$, for the identification and assignment of the individual protons. Fig. 4 shows the contour plot of the proton COSY-45 spectrum. The interpretation of these spectra is based on the unambiguous assignment of the H-41 and C-2 protons.

The COSY cross-connectivity patterns reveal that there is no correlation between H-41 and the signals contained in the low-field region, between 2.40 and 3.40 ppm; hence, we can assign these multiplets to the C-2, C-6 and C-7 protons, while the high-field signals at ca. 1.31, 1.40 and 2.17 ppm must correspond to the C-5 and

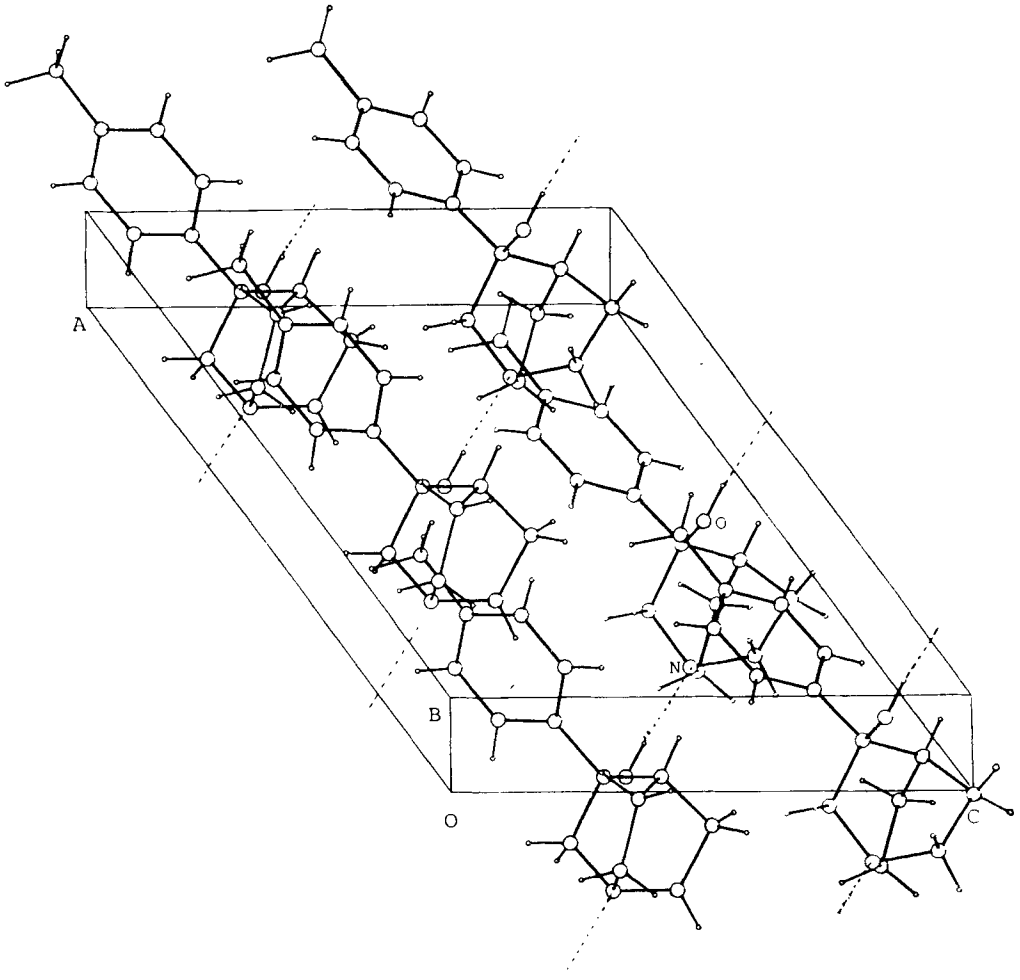

Figure 2. View of the molecular packing in the unit cell of **1**.

C-8 protons owing to their observed correlations with H-41.

The observation of two NOESY cross-peaks at $\delta = 2.07/7.32$ ppm (weak) and $\delta = 3.29/7.32$ ppm (stronger) points out the expected proximity of the H-41 proton with the H-10(14) aromatic protons, and leads to the conclusion that the lowest doublet of doublets at 3.29 ppm must correspond to H-22 (Scheme 1). The other upfield doublet of doublets at 2.88 ppm can therefore be assigned to H-21.

The H-72 proton is assigned to the multiplet at ca. 2.72 ppm on the basis of its correlation with H-22, which indicates a 'W' long-range coupling[33] between these protons. A large correlation is observed between H-72 and the signal centred at ca. 2.88 ppm, and the H-71 proton resonance must therefore be partially overlapped with the H-21 signal, while the C-6 protons resonate at ca. 2.58 ppm. Further, the COSY connectivity patterns show that there are 'W' long-range couplings between the C-6 protons and H-21 and H-71.

The assignment of the C-5 and C-8 proton resonances is confirmed on the basis of their large correlations with the C-6 and C-7 protons. H-51 and H-52, as well as H-81 and H-82, are distinguished by the observation of a weak cross-peak at $\delta = 2.17/1.31$ ppm (four-bond 'W' coupling) which, therefore, permits the tentative assignment of H-51 to the highest-field signal and H-81 to the proton absorbing at 2.17 ppm, while H-52 should overlap with H-82 at ca. 1.40 ppm.

To strengthen these assumptions, double resonance (DR) experiments were performed at 300 MHz. Thus, the saturation of the resonance frequency of the C-6 protons shows the loss of a coupling of approximately 2.0 Hz at H-21 and H-71. Moreover, the multiplet at ca. 1.40 ppm becomes simplified, and the highest-field multiplet simplifies into a doublet of triplets with splittings of ca. 13.0 and 2.8 Hz. There is no doubt, therefore, about the assignment of the resonance at 1.31 ppm to H-51, which exhibits similar couplings with H-41 and H-81. Further interpretation of DR experiments in which the resonance frequency of H-22, H-72, H-81 and H-41 are saturated confirm the above considerations about the assignment of the signals.

A similar behaviour can be assumed bearing in mind the similarity of the ^{1}H NMR spectra for the 3-aryl-3-quinuclidinols **1**–**4** and the DR experiments, performed in all cases. This allows the complete and unambiguous assignment of the individual protons for the bicyclic system of compounds **1**–**4**, except for H-61 and H-62 which cannot be distinguished clearly and overlap as ill-resolved multiplets.

The proton magnetic parameters of compounds **1**–**4** were deduced by analysis of the 300 MHz spectra, taking into account the coupling modifications

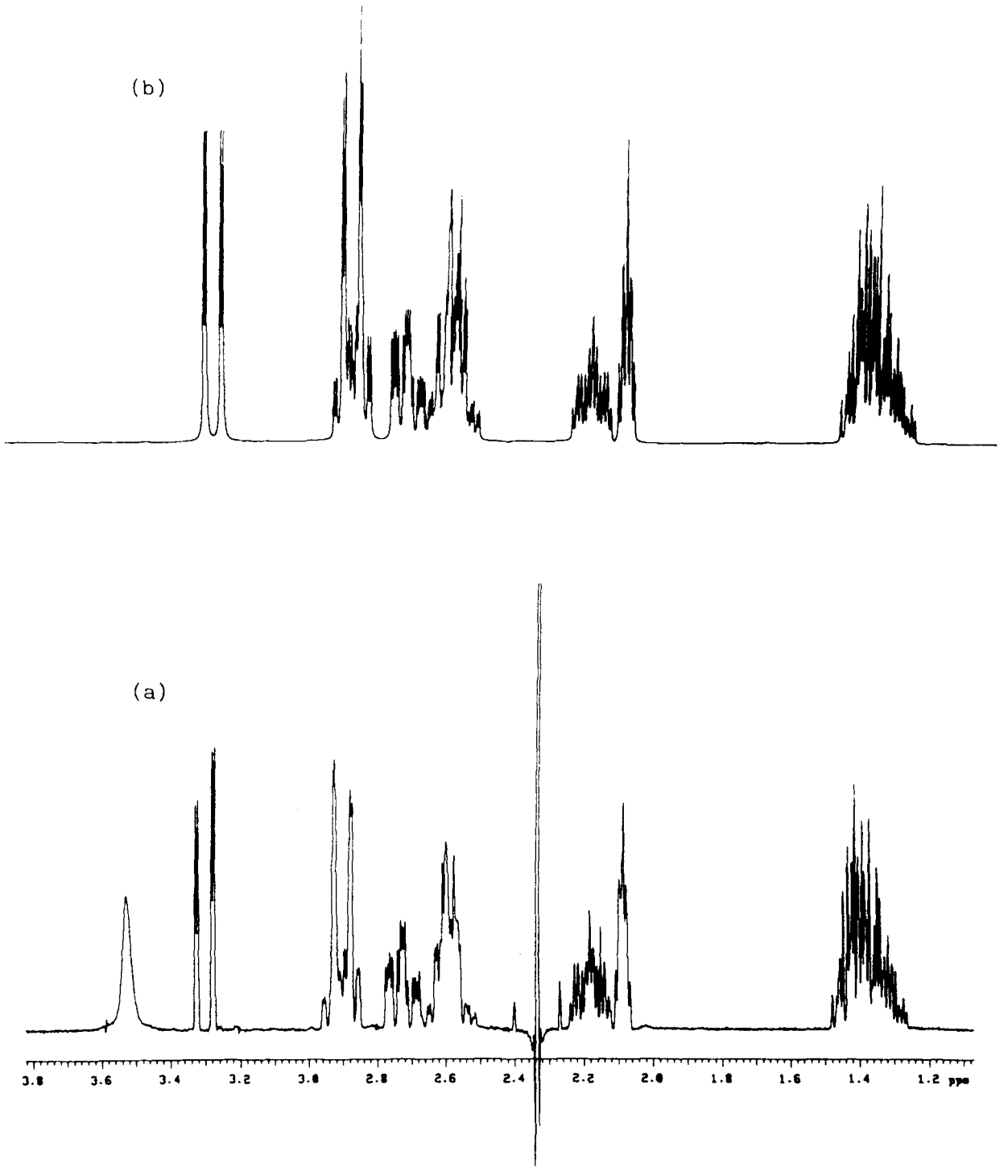

Figure 3. (a) 300 MHz ^{1}H NMR spectrum of **1** in $CDCl_3$ (the aromatic region is omitted); (b) simulated spectrum.

observed in the different DR experiments. The multiplets corresponding to H-51, H-52; H-71, H-72; H-81 and H-82 were considered as parts of the respective six spin systems whose analysis were carried out with the LAOCOON III program.[20] The values of the optimized magnetic parameters, together with the most probable errors, are shown in Tables 5 and 6.

The H-21 and H-22 doublets of doublets were considered as parts of the respective three-spin AMX systems formed by H-21, H-22, H-62 and H-21, H-22, H-72, respectively, whose first-order analysis led to the establishment of δH-21, δH-22, ^2J(H21, H22) and ^4J(H-21, H-62) (Tables 5 and 6). The ill-resolved multiplets corresponding to the H-41 and C-6 protons could not be analyzed and their chemical shifts were estimated as the centres of the respective signals. Nevertheless, from the adjustment of H-51 and H-52 a limiting value of the order of 15 Hz was deduced for $|\Delta\nu$H62–H61$|$.

The aromatic protons absorb as four-spin AA'MM' systems, except for **4** (Y = F). In the latter case the signals were considered as parts of the five-spin AA'MM'X system formed by the aromatic protons and

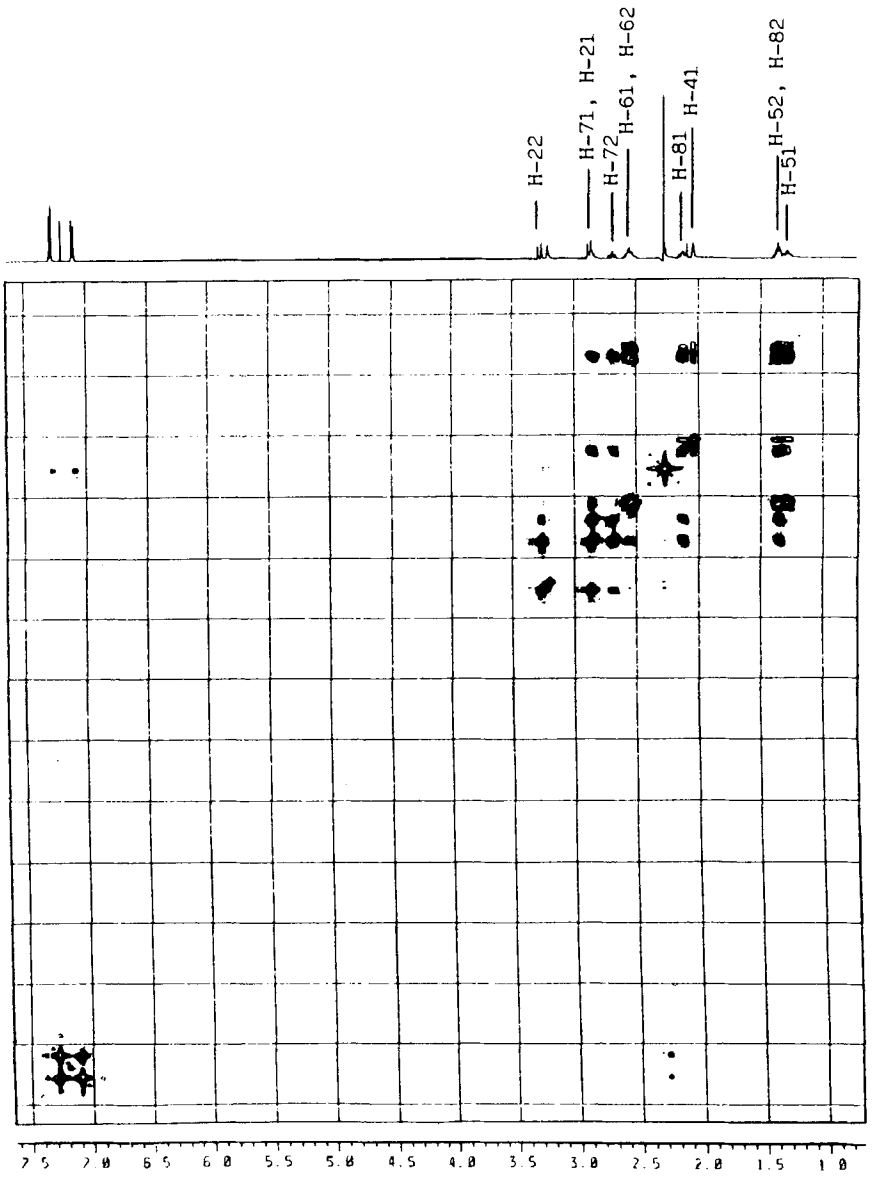

Figure 4. Contour plot of the 500 MHz proton COSY-45 spectrum of **1** in $CDCl_3$.

Table 5. ^{1}H chemical shifts for (±)-3-aryl-1-azabicyclo[2.2.2]octan-3-ols (1–4)

Chemical shifts[a] δ (ppm)	**1** (Y = CH_3)	**2** (Y = OCH_3)	**3** (Y = Cl)	**4** (Y = F)
H-22 (dd)	3.29	3.44	3.23	3.38
H-21 (dd)	2.88	3.05	2.87	3.01
H-71 (m)	2.876 (0.001)	2.995 (0.001)	2.868 (0.001)	2.955 (0.001)
H-72 (m)	2.723 (0.001)	2.844 (0.001)	2.705 (0.001)	2.803 (0.001)
H-61 (m)[b]	2.55	2.68	2.54	2.64
H-62 (m)[b]	2.61	2.73	2.60	2.69
H-81 (m)	2.166 (0.001)	2.219 (0.001)	2.163 (0.001)	2.201 (0.001)
H-41 (q apparent)	2.07	2.17	2.04	2.13
H-52 (m)	1.415 (0.001)	1.491 (0.001)	1.435 (0.001)	1.487 (0.001)
H-82 (m)	1.397 (0.001)	1.471 (0.001)	1.406 (0.001)	1.457 (0.001)
H-51 (m)	1.312 (0.001)	1.376 (0.001)	1.272 (0.001)	1.336 (0.001)
OH (s)	3.50	2.56	3.50	3.13
CH_3	2.32 (s)	3.79 (s)	—	—
H-10 (14) (m)	7.32	7.381 (0.001)	7.301 (0.001)	7.45
H-11 (13) (m)	7.14	6.870 (0.001)	7.360 (0.001)	7.05

[a] Abbreviations: dd, doublet of doublets; m, multiplet; q, quintet; s, singlet; δ values were deduced from the analysis of the spectra with an error of ±0.01 ppm, except for indicated cases (in parentheses) where they have been calculated by means of the LAOCOON III program.
[b] Tentative assignment.

Table 6. ^{1}H-^{1}H coupling constants for (±)3-aryl-1-azabicyclo[2.2.2]octan-3-ols (1–4)

Coupling Constants J (Hz)	1 (Y = CH_3)	2 (Y = OCH_3)	3 (Y = Cl)	4 (Y = F)[a]
^2J				
H21–H22	−14.4 (0.1)	−14.4 (0.1)	−14.4 (0.1)	−14.4 (0.1)
H51–H52	−13.24 (0.03)	−13.40 (0.06)	−13.09 (0.08)	−13.35 (0.04)
H71–H72	−12.96 (0.03)	−13.04 (0.06)	−13.10 (0.08)	−13.20 (0.04)
H81–H82	−13.06 (0.03)	−12.92 (0.06)	12.96 (0.04)	−13.15 (0.04)
^3J				
H41–H51	2.87 (0.03)	2.96 (0.04)	3.01 (0.04)	3.16 (0.03)
H41–H52	3.98 (0.03)	4.07 (0.04)	4.21 (0.04)	3.82 (0.03)
H41–H81	3.76 (0.03)	3.51 (0.04)	3.68 (0.04)	3.83 (0.03)
H41–H82	2.74 (0.03)	2.40 (0.04)	2.45 (0.04)	2.45 (0.03)
H51–H61	10.07 (0.03)	9.70 (0.04)	10.00 (0.04)	10.03 (0.03)
H51–H62	6.64 (0.03)	7.00 (0.04)	6.74 (0.04)	6.56 (0.03)
H52–H61	4.79 (0.03)	4.91 (0.04)	4.66 (0.04)	4.59 (0.03)
H52–H62	9.95 (0.03)	9.78 (0.04)	10.45 (0.04)	10.16 (0.03)
H71–H81	9.98 (0.03)	9.61 (0.04)	10.20 (0.04)	10.19 (0.03)
H71–H82	6.62 (0.03)	6.43 (0.04)	6.68 (0.04)	6.49 (0.03)
H72–H81	3.70 (0.03)	3.77 (0.04)	3.78 (0.04)	3.61 (0.03)
H72–H82	10.30 (0.03)	10.69 (0.04)	10.50 (0.04)	10.60 (0.03)
H10–H11	8.3 (0.1)[b]	8.91 (0.08)	8.90 (0.08)	8.8 (0.1)[b]
$\lvert^4J\rvert$				
H21–H62	2.0 (0.1)	≤2.0[c]	1.9 (0.1)	1.9 (0.1)
H22–H72	2.09 (0.03)	2.01 (0.04)	1.94 (0.04)	2.18 (0.03)
H51–H81	2.75 (0.03)	2.83 (0.04)	2.89 (0.04)	2.84 (0.03)
H61–H71	2.20 (0.03)	≤2.0[c]	2.09 (0.04)	2.20 (0.03)
H10–H14	—[b]	2.74 (0.08)	2.25 (0.08)	—[b]

[a] ^3J(H11, F) = ^3J(H13, F) = 8.1 Hz; $\lvert^4J$(H10, F)$\rvert$ = $\lvert^4J$(H14, F)$\rvert$ = 5.3 Hz.
[b] For **1** and **4** only ^3J(H10, H-11) = ^3J(H13, H14) could be determined assuming ^5J(H10, H13) = ^5J(H11, H14) = 0 Hz as for **2** and **3**.
[c] These 'W' long-range coupling constants were not observed, and a limiting value of ca. 2.0 Hz has been estimated on the basis of the line width of the signals.

the fluorine atom. The analysis of the corresponding signals for **2** and **3** by means of the LAOCOON III program[20] allowed the establishment of the chemical shifts (Table 5) and coupling constants ^3J(H10, H11) ^3J(H13, H14), ^4J(H10, H14) ^4J(H11, H13) and ^5J(H10, H13) = ^5J(H11, H14) = 0 Hz (Table 6).

The ^{13}C NMR chemical shifts are tabulated, with the signal assignments, in Table 7. Substituent steric and electronic effects on the ^{13}C chemical shifts[34,35] and the signal multiplicity obtained from the DEPT experiments[14] were taken into consideration. A distinction could be made between the chemical shift values of C-5 and C-8, as well as between those of C-6 and C-7, from the heteronuclear ^{1}H-^{13}C shift correlation spectrum of **1** (Fig. 5), once the resonances of the respective protons were known. Moreover, the heteronuclear ^{1}H-^{13}C correlated spectrum confirms the previous considerations about the proton assignments.

Therefore, 2D NMR techniques provide an useful means for the establishment of the magnetic parameters of these 3-aryl-1-azabicyclo[2.2.2]octan-3-ols. COSY-45, NOESY and heteronuclear ^{1}H–^{13}C correlation experiments allowed the assignment of all bicyclic proton and carbon resonances.

Furthermore, the observed ^{1}H–^{1}H coupling constants of the quinuclidine moiety are very similar (Table 6) and can be considered as standard values for analysing more complex quinuclidine derivatives which are structurally related to those studied.

Table 7. ^{13}C Chemical shifts for (±)-3-aryl-1-azabicyclo[2.2.2]octan-3-ols (1–4)

Chemical shifts[a] δ (ppm)	1 (Y = CH_3)	2 (Y = OCH_3)	3 (Y = Cl)	4 (Y = F)[b]
C-8	21.48	21.26	21.53	21.50
C-5	23.10	22.82	23.07	23.05
C-4	32.69	32.85	33.01	32.95
C-6	45.73	45.47	45.88	45.82
C-7	46.71	46.52	46.83	46.74
C-2	62.18	61.83	62.30	62.41
C-3	71.82	71.28	71.76	71.69
C-10 (14)	126.06	127.09	127.62	127.72
C-11 (13)	128.69	113.18	128.31	114.81
C-12	136.40	158.21	132.94	161.77
C-9	143.59	138.73	145.42	142.56
CH_3	20.81	55.03	—	—

[a] Directly measured from the spectra. Error ±0.02 ppm.
[b] J(C, F) coupling constants: ^1J = 246.34 Hz; $\lvert^2J\rvert$ = 20.97 Hz; ^3J = 7.88 Hz; $\lvert^4J\rvert$ = 3.13 Hz.

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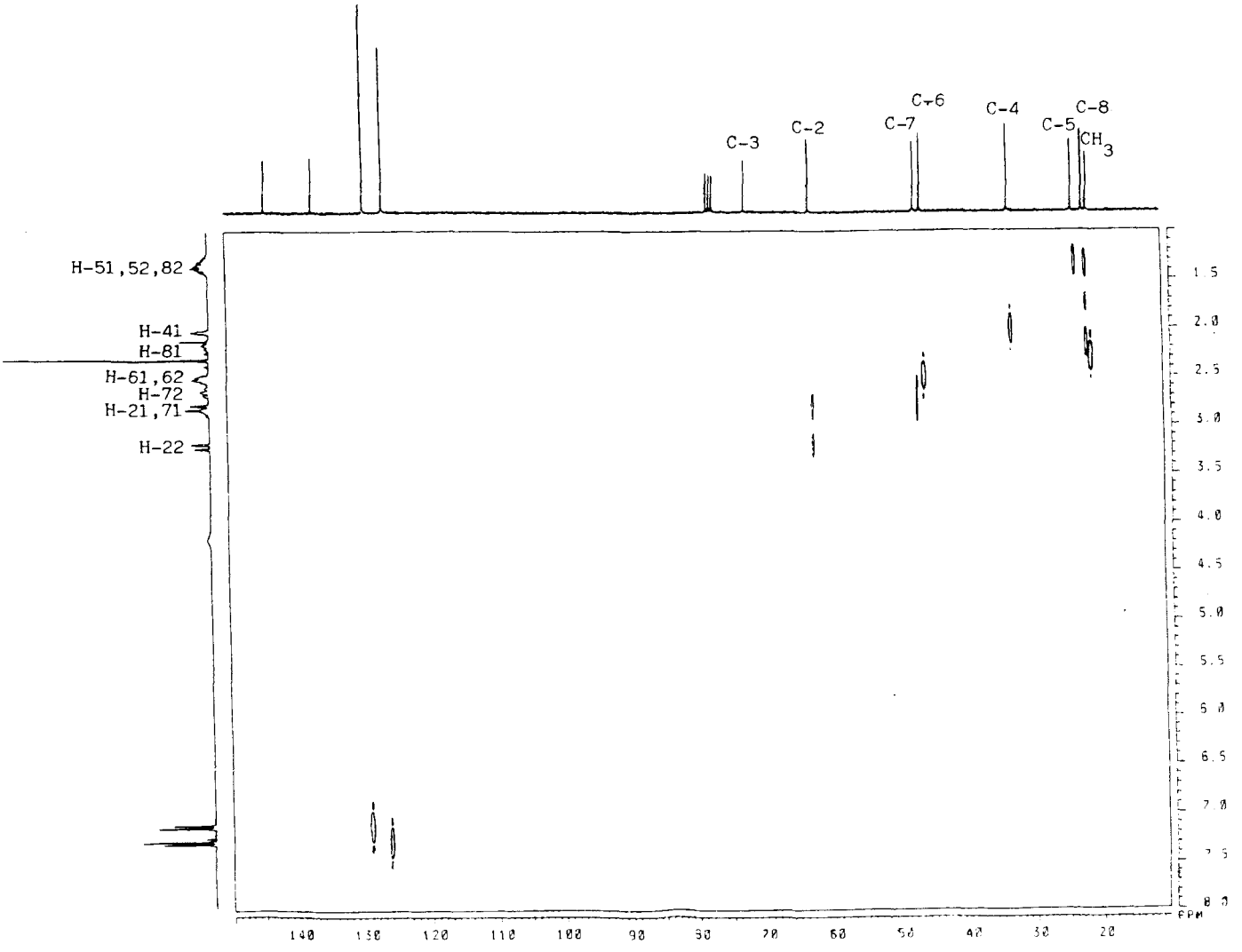

Figure 5. ^{1}H-^{13}C correlated spectrum of **1** in $CDCl_3$.

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