Substituent Effects in Various Alkyl Derivatives of 9a*H*-Quinolizine-1,2,3,4-tetracarboxylate Studied by ^{13}C NMR Spectroscopy and X-Ray Analysis

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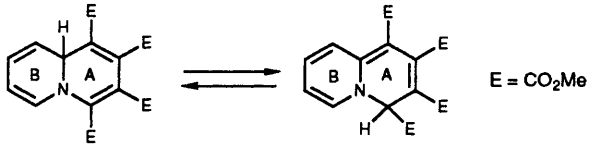
The ^{13}C NMR spectra of 22 alkyl-substituted 9a*H*-quinolizine-1,2,3,4-tetracarboxylates have been obtained and X-ray analyses have been performed for three of them. The chemical shift differences between the parent 9a*H*-quinolizine and the methyl-substituted compounds can only be interpreted in terms of the usual α and β effects for 8-methyl-9a*H*-quinolizine. 6-, 7-, 9-, and 9a-methyl substituents cause not only a very large deshielding of the carbon at the position of substitution together with shielding changes at adjacent atoms, but also influence the shieldings of the other carbons in both rings of the compounds under study. The observed changes are interpreted in terms of steric hindrance between the methyl groups of ring B and the ester groups of ring A, and hyperconjugative effects introduced by the methyl groups.

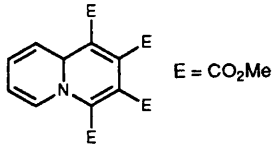
9a*H*-Quinolizine-1,2,3,4-tetracarboxylate was first synthesized by Diels and Alder in 1932[1] and since then this compound and its various methyl derivatives have been the subject of numerous studies.[2–6] The most interesting feature of this group of compounds is that their rates of conversion into the more thermodynamically stable 4*H*-tautomers depend on the position of methyl groups in the ring B (Scheme 1).



Scheme 1.

The tautomerization barrier is high enough for the 9-methyl substituted compounds to render them stable at room temperature.[2,3] Thus, they are easily acccessible to investigation. The 6-methyl compounds are also relatively stable at room temperature. The parent 9a*H*-quinolizine-1,2,3,4-tetracarboxylate, on the other hand, converts very quickly into the 4*H*-tautomer, even at temperatures <0 °C.[7] Since 1932 its synthesis has been repeated no more than three times.[6–8] The 7-and 8-methyl quinolizines have eluded until now all attempts at synthesis.[3,4] This is the reason why all references cited (except for reference 6) discuss the data only for those quinolizines with methyl groups at C9 and C6 and for the C9a methyl-substituted compounds. The latter, for obvious reasons, cannot undergo the 9a*H* ⇄ 4*H* tautomerization. The lack of 7- and 8-methyl compounds has made interpretation of the data obtained for the remaining compounds difficult.[6]

In the present paper we report ^{13}C NMR results for the parent 9a*H*-quinolizine-1,2,3,4-tetracarboxylate (**1**), for all five possible monomethyl substituted 9a*H*-quinolizines (**2**)–(**6**) including the most unstable, for the series of substituted dimethyl and trimethyl compounds (**7**)–(**17**), and for the corresponding ethyl-substituted compounds (**18**)–(**22**). The data for compounds (**1**), (**2**), (**5**), (**6**), (**10**), (**12**), and (**15**) are taken from our previous paper.[6] For 6-methyl- (**2**), 9a-methyl- (**6**), and 7,9-dimethyl- (**12**) quinolizines, which are stable at room temperature, X-ray analyses have also been performed.



(**1**)

Substituted derivatives ‡

(**2**) 6-methyl	(**9**) 6,9-dimethyl	(**16**) 9,9a-dimethyl
(**3**) 7-methyl	(**10**) 6,9a-dimethyl	(**17**) 6,8,9a-trimethyl
(**4**) 8-methyl	(**11**) 7,8-dimethyl	(**18**) 6-ethyl
(**5**) 9-methyl	(**12**) 7,9-dimethyl	(**19**) 7-ethyl
(**6**) 9a-methyl	(**13**) 7,9a-dimethyl	(**20**) 8-ethyl
(**7**) 6,7-dimethyl	(**14**) 8,9-dimethyl	(**21**) 9-ethyl
(**8**) 6,8-dimethyl	(**15**) 8,9a-dimethyl	(**22**) 9a-ethyl

The results are discussed in terms of additivity effects and the influence of methyl groups on the ^{13}C chemical shifts and electron distribution in the compounds studied.

Experimental

All compounds were obtained *via* the Diels–Alder condensation.[1] Dimethyl acetylenedicarboxylate and pyridine and its methyl and ethyl derivatives were the starting materials. The compounds (**2**),† (**5**), (**6**), (**9**), (**10**), (**12**)–(**16**), (**18**), (**21**), and (**22**), which are all stable at room temperature, were synthesized, isolated and purified as described by Acheson and co-workers.[9,10] The m.p.s of these compounds are given below (in °C) together with literature values (in parentheses) for the known compounds and analyses for the unknown ones: (**2**) 126

† Pure compound (**2**) is stable at room temperature as described by Acheson.[10] During the work-up process, however, a substantial part of it isomerizes into the 4*H* form. The 9a*H* ⇄ 4*H* tautomerization at room temperature has never been observed for the 9-methyl substituted compound.

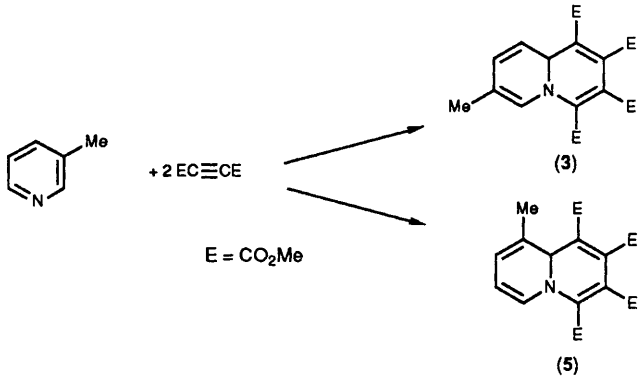
‡ The numbering for this system is given in Figure 2.

(126[10]); (**5**) 121–122 (121–122[9]); (**6**) 140 (140[10]); (**9**) 130.5–131.5 (C, 58.3; H, 5.4; N, 3.5); (**10**) 103–104 (103[10]); (**12**) 141–142 (141–142[9]); (**13**) 41–42 (C, 58.4; H, 5.5; N, 3.5); (**14**) 120.5–121.5 (C, 58.3; H, 5.5; N, 3.3); (**15**) 123–124 (123–124[6]); (**16**) 94 (C, 58.5; H, 5.4; N, 3.5); (**18**) 125 (125[10]); (**21**) 99.5 (C, 58.5; H, 5.4; N, 3.5); (**22**) 116 (116[10]). For all compounds analysed, the formula $C_{19}H_{21}NO_8$ requires: C, 58.3; H, 5.4; N, 3.6%.

The remaining compounds, *i.e.*, the parent 9a*H*-1,2,3,4-tetracarboxylate (**1**) and the 7-methyl- (**3**), 8-methyl- (**4**), 6,7-dimethyl- (**7**), 6,8-dimethyl- (**8**), 7,8-dimethyl- (**11**), 7-ethyl-(**19**), and 8-ethyl-(**20**) 9a*H*-quinolizines, were prepared by means of the procedure described in our first paper of this series for the parent 9a*H*-quinolizine (**1**).[6]

The compounds (**4**) and (**20**) which are the only products from the reaction of dimethyl acetylenedicarboxylate with 4-methyl- and 4-ethylpyridine, respectively, were purified by means of TLC on neutral alumina plates and identified by means of IR, UV, and ^{1}H NMR spectroscopy. For both compounds, IR bands at 1 740, 1 700, 1 618, 1 520, 1 438, and 1 408 cm^{-1} were observed. Two UV bands at λ_{max} (in dioxane) 285 and 430 nm were found. δ_H ($CDCl_3$) for (**4**): 6.40–6.33 (1 H, d, 6-H), 5.73–5.64 (1 H, dd, 7-H), 1.84–1.81 (3 H, t, 8-Me), 5.27 (1 H, m, 9-H), and 4.78–4.73 (1 H, m, 9a-H). δ_H ($CDCl_3$) for (**20**): 6.44–6.37 (1 H, d, 6-H), 5.77–5.68 (1 H, dd, 7-H), 1.09–0.95 (3 H, t, 8-CH_2CH_3), 2.24–2.03 (2 H, q, 8-CH_2CH_3), 5.27 (1 H, br s, 9-H), and 4.75 (1 H, br s, 9aH). All spectra obtained are characteristic of 9a*H*-quinolizines.[6]

Compounds (**3**), (**7**), (**8**), (**11**), and (**19**) are always formed as mixtures together with the second possible 9a*H*-isomer as shown, *e.g.* for 3-methylpyridine in Scheme 2 below.



Scheme 2.

The retention time for TLC and the solubilities of (**3**), (**7**), (**11**), and (**19**), and their corresponding counterparts *i.e.* (**5**), (**16**), (**14**), and (**21**), respectively, are practically identical which makes the separation of a given pair impossible. Therefore, the following procedure was applied to obtain the spectra of this group of compounds. The pairs (**3**) and (**5**), (**7**) and (**16**), (**19**) and (**21**) were isolated from the reaction mixture, as described in ref. 6, and purified on alumina plates with no attempt to separate them. An analogous procedure was applied for the pair (**11**) and (**14**), but because of the instability of compound (**11**) (7,8-dimethyl-9a*H*-quinolizine) the whole synthesis, including the work-up, was carried out at a temperature close to 0 °C. The ^{13}C NMR spectra of the unresolved pairs were recorded. The compounds (**3**), (**7**), (**11**), and (**19**) were then converted into their 4*H*-tautomers, which allowed a facile separation from the 9a*H*-quinolizines (**5**), (**16**), (**14**), and (**21**), respectively. The conversion of (**11**) was very quick—within a few hours—and only the standard proton decoupled ^{13}C NMR spectrum was recorded for the pair (**11**) and (**14**). It was, however, impossible to record the long-run spectra, *e.g.* we were not able to measure for this sample, the ^{1}H-coupled ^{13}C spectra with NOE retained. The conversion of (**3**) and (**19**) into the 4*H* forms was achieved by leaving the samples in $CHCl_3$ solutions at room temperature for two or three days. The mixture of (**7**) and (**16**) was boiled for three days in $CHCl_3$ until a full conversion of (**7**) into the 4*H* tautomer took place. The resulting mixtures of 4*H* and 9a*H* compounds were separated on alumina plates using a mixture of acetic ester–hexane (2:3) as eluant and the spectra of isolated, pure (**5**), (**16**), (**14**), and (**21**) were recorded and compared with the spectrum of the mixture. A comparison of the spectra recorded before and after conversion of one component of the mixture into the 4*H* form provided a straightforward assignment of the signals to the particular isomer in each pair of the 9a*H*-quinolizines.

6,8-Dimethyl-9a*H*-quinolizine (**8**) was easily separated on alumina plates from its stable 8,9a- counterpart (**15**) but because of the great instability of this compound it could only be characterized by IR, UV, and ^{1}H NMR spectroscopy as follows: ν_{max} 1 740, 1 700, 1 618, 1 520, 1 438, and 1 408 cm^{-1}; λ_{max} 285 and 430 nm; δ_H 1.94 (3 H, s, 6-Me), 5.76 (1 H, s, 7-H), 1.81–1.77 (3 H, t, 8-Me), 5.30 (1 H, br s, 9-H), and 4.95 (1 H, br s, 9a-H). The same is true of 6,8,9a-trimethyl-9a*H*-quinolizine (**17**), the fast decomposition of which led to rather poor results in the elemental analysis. However, IR, UV, and ^{1}H NMR spectroscopy fully confirmed the structure of this compound.

The ^{1}H and ^{13}C NMR spectra were recorded for samples in 5 mm tubes with a Bruker WP-100 SY instrument. Samples were dissolved in $CDCl_3$ at 1 mol dm^{-3}, and TMS was used as an internal reference. Typical conditions used to record the ^{13}C spectra were as follows: 30° pulse, acquisition time 1.1 s, relaxation delay 0.4 s, digital resolution 0.4 Hz per point. For all compounds the DEPT spectra were recorded routinely. For all compounds apart from (**11**) the ^{1}H-coupled ^{13}C spectra with NOE retained were measured using routine gated decoupling. For sample (**5**) the heteronuclear shift-correlated 2D NMR spectrum (CPD decoupling) using polarization transfer from ^{1}H to X *via* J(XH)[11] was recorded with a Bruker AM 500 spectrometer.

Table 1. Crystallographic data and measurement conditions.

Compound	(**2**)	(**6**)	(**12**)
Formula	$C_{18}H_{19}NO_8$	$C_{18}H_{19}NO_8$	$C_{19}H_{21}NO_8$
M	377.35	377.35	391.38
a/Å	8.086(2)	21.809(3)	9.232(1)
b/Å	14.194(4)	9.055(1)	10.518(1)
c/Å	16.470(3)	18.755(2)	10.628(2)
α/°	90.0	90.0	91.00(1)
β/°	101.81(1)	90.0	92.38(2)
γ/°	90.0	90.0	111.63(1)
V/Å^3	1 850.3(8)	3 703.8(8)	957.9(2)
Space group	$P2_1/n$	$Pbcn$	$P\bar{1}$
Z	4	8	2
D_x/g cm^{-1}	1.35	1.35	1.36
Diffractometer	CAD4	CAD4	CAD4
Radiation/Å	1.541 78	1.541 78	1.541 78
μ(Cu-K_α)/mm^{-1}	0.87	0.72	0.67
Scan mode	θ/2θ	θ/2θ	θ/2θ
$2\theta_{max}$/°	140	140	140
h, k, l_{max}	9, 15, 18	24, 10, 20	10, 11, 11
No. of reflections (total) measured	3 097	3 256	3 015
No. of reflections (3σ) (unique)	2 199	2 045	2 253
Weights	$1/\sigma^2$	$1/\sigma^2$	$1/\sigma^2$
R	0.044	0.049	0.044
R_w	0.058	0.058	0.044

Table 2. Fractional atomic co-ordinates ($\times 10^4$) compounds (**2**), (**6**), and (**12**) (esds in parentheses).

	(2)			(6)			(12)		
	x/a	*y/b*	*z/c*	*x/a*	*y/b*	*z/c*	*x/a*	*y/b*	*z/c*
C(1)	3 937(2)	1 270(1)	−268(1)	1 588(1)	3 740(3)	3 712(1)	460(3)	4 987(3)	8 156(2)
C(2)	4 254(3)	1 825(2)	410(1)	1 107(2)	2 875(3)	3 856(1)	312(3)	3 671(3)	8 113(2)
C(3)	5 400(3)	2 625(2)	448(1)	825(1)	2 914(3)	4 561(1)	−1 175(3)	2 592(2)	7 730(2)
C(4)	6 424(3)	2 654(1)	−121(1)	1 156(1)	3 537(2)	5 101(1)	−2 432(3)	2 977(2)	7 516(2)
N(5)	6 306(2)	2 017(1)	−736(1)	1 698(1)	4 245(2)	4 983(1)	−2 332(2)	4 274(2)	7 574(2)
C(6)	7 318(3)	2 019(2)	−1 358(1)	2 073(1)	4 696(3)	5 545(1)	−3 617(3)	4 686(3)	7 298(2)
C(7)	6 459(4)	2 053(2)	−2 140(1)	2 640(1)	5 198(3)	5 433(2)	−3 395(3)	5 752(3)	6 582(2)
C(8)	4 645(4)	2 146(2)	−2 324(1)	2 879(1)	5 242(3)	4 723(2)	−1 906(3)	6 334(3)	5 985(3)
C(9)	3 753(3)	1 870(2)	−1 774(1)	2 514(1)	5 033(3)	4 171(2)	−621(3)	6 183(3)	6 453(2)
C(9a)	4 779(3)	1 430(2)	−991(1)	1 830(1)	4 849(3)	4 251(1)	−825(3)	5 454(2)	7 706(2)
C(10)	2 801(2)	444(2)	−315(1)	1 863(1)	3 774(3)	2 984(1)	1 917(3)	6 072(3)	8 668(3)
O(11)	2 305(2)	104(1)	260(1)	1 877(1)	4 853(3)	2 616(1)	3 085(3)	5 896(2)	9 001(3)
O(12)	2 372(2)	126(1)	−1 091(1)	2 071(1)	2 460(3)	2 785(1)	1 795(2)	7 286(2)	8 705(2)
C(13)	1 233(4)	−669(2)	−1 210(2)	2 261(3)	2 322(8)	2 047(2)	3 192(4)	8 438(3)	9 108(3)
C(14)	3 450(3)	1 611(2)	1 135(1)	891(1)	1 794(3)	3 307(1)	1 715(3)	3 301(3)	8 408(3)
O(15)	2 071(2)	1 861(1)	1 190(1)	726(1)	2 119(2)	2 719(1)	2 590(2)	3 245(2)	7 635(2)
O(16)	4 497(2)	1 102(1)	1 694(1)	925(1)	425(2)	3 557(1)	1 844(2)	3 052(2)	9 619(2)
C(17)	3 819(5)	785(2)	2 395(2)	689(3)	−741(5)	3 106(3)	3 235(4)	2 796(4)	9 990(3)
C(18)	5 414(3)	3 347(2)	1 090(1)	208(1)	2 340(3)	4 710(1)	−1 433(3)	1 146(3)	7 600(3)
O(19)	4 853(2)	3 239(2)	1 702(1)	−13(1)	2 221(3)	5 294(1)	−2 640(3)	257(2)	7 251(2)
O(20)	6 080(2)	4 159(1)	905(1)	−89(1)	2 012(2)	4 113(1)	−191(3)	876(2)	7 940(3)
C(21)	6 156(4)	4 914(2)	1 503(2)	−699(1)	1 410(5)	4 186(2)	−252(5)	−509(4)	7 771(6)
C(22)	7 780(3)	3 400(1)	−97(1)	954(1)	3 416(3)	5 871(1)	−4 083(3)	1 946(3)	7 287(3)
O(23)	7 738(2)	3 988(1)	−615(1)	1 091(1)	2 423(2)	6 256(1)	−4 920(2)	1 443(2)	8 108(2)
O(24)	9 021(2)	3 259(1)	556(1)	644(1)	4 617(2)	6 048(1)	−4 488(2)	1 761(2)	6 069(2)
O(25)	10 417(3)	3 913(2)	643(2)	396(2)	4 647(5)	6 765(2)	−6 089(4)	835(4)	5 789(3)
6-Me	9 186(4)	1 919(2)	−1 092(2)	—	—	—	—	—	—
7-Me	—	—	—	—	—	—	−4 672(4)	6 283(3)	6 304(3)
9-Me	—	—	—	—	—	—	911(4)	6 670(3)	5 835(3)
9a-Me	—	—	—	1 503(2)	6 346(3)	4 179(2)	—	—	—

Table 3. Interatomic distances/Å for compounds (**2**), (**6**), and (**12**)

	6-Me (**2**)	9a-Me (**6**)	7,9-di-Me (**12**)
C(2)–C(1)	1.348(3)	1.337(3)	1.340(5)
C(9a)–C(1)	1.505(3)	1.519(3)	1.507(4)
C(10)–C(1)	1.482(3)	1.492(3)	1.482(3)
C(3)–C(2)	1.459(4)	1.459(3)	1.459(3)
C(14)–C(2)	1.503(3)	1.497(3)	1.507(5)
C(4)–C(3)	1.372(3)	1.366(3)	1.375(4)
C(18)–C(3)	1.471(3)	1.469(3)	1.453(4)
N(5)–C(4)	1.346(2)	1.363(3)	1.333(3)
C(22)–C(4)	1.519(3)	1.514(3)	1.517(3)
C(6)–N(5)	1.436(3)	1.395(3)	1.427(4)
C(9a)–N(5)	1.477(3)	1.506(3)	1.483(3)
C(7)–C(6)	1.333(2)	1.334(3)	1.326(4)
C(8)–C(7)	1.442(4)	1.431(5)	1.462(4)
C(9)–C(8)	1.327(4)	1.320(5)	1.332(4)
C(9a)–C(9)	1.518(3)	1.508(3)	1.537(3)
O(11)–C(10)	1.203(3)	1.197(3)	1.200(4)
O(12)–C(10)	1.333(2)	1.327(4)	1.323(4)
C(13)–O(12)	1.444(3)	1.450(5)	1.449(3)
O(15)–C(14)	1.191(3)	1.197(3)	1.194(4)
O(16)–C(14)	1.329(3)	1.327(3)	1.333(4)
C(17)–O(16)	1.447(4)	1.447(6)	1.447(5)
O(19)–C(18)	1.197(3)	1.201(3)	1.200(3)
O(20)–C(18)	1.334(3)	1.327(3)	1.318(4)
C(21)–O(20)	1.448(3)	1.444(3)	1.445(5)
O(23)–C(22)	1.189(2)	1.191(3)	1.190(4)
O(24)–C(22)	1.327(2)	1.323(3)	1.329(4)
C(25)–O(24)	1.446(3)	1.450(4)	1.454(3)
6(Me)–C(6)	1.491(4)	—	—
7(Me)–C(7)	—	—	1.501(5)
9(Me)–C(9)	—	—	1.501(4)
9a(Me)–C(9a)	—	1.538(4)	—

X-Ray Analysis.—Well-shaped crystals of compounds (**2**), (**6**), and (**12**), of diameters not >0.4 mm, were chosen for data collection on the Enraf-Nonius diffractometer.

Unit-cell parameters refined against 25 reflections, and information concerning the refinement procedure are presented in Table 1. Intensities of reflections were corrected for Lorentz and polarization factors. After isotropic refinement in the presence of the calculated hydrogen atom positions, they were further corrected for the experimental spherical absorption effect by means of the DIFABS program.[12] Structures were solved by direct methods (SHELX 86)[13] and refined by a full-matrix least-squares procedure (SHELX 76-G).[14] The positions of the hydrogen atoms were found from ΔF maps and refined. Positional parameters for non-hydrogen atoms are given in Table 2, and Table 3 lists interatomic distances. Stereopictures of the molecules are presented in Figure 1. The crystallographic numbering scheme and conformational details of the molecules are shown in Figure 2. A conformational analysis of the rings is given in Table 4. Tables of fractional co-ordinates, bond lengths, bond angles, torsion angles, and isotropic equivalent temperature factors for compounds (**2**), (**6**), and (**12**) have been deposited at the Cambridge Crystallographic Data Centre (CCDC).*

Results and Assignments.—The X-ray data obtained for 6-methyl- (**2**), 9a-methyl- (**6**), and 7,9-dimethyl- (**12**) 9a*H*-quinolizine tetracarboxylates are collected in Tables 1–4 and presented in Figures 1 and 2. The contents of the Tables are described in detail in the Experimental section (see above for the

* For details, see 'Instructions for Authors (1990),' *J. Chem. Soc., Perkin Trans. 2*, in the January issue.

Table 4. Conformation of the A and B rings in (**2**), (**6**), and (**12**).

	(2)		(6)		(12)	
	A	B	A	B	A	B
Asymmetry parameters[a]						
C_2(C2–C3)/°	2.2	—	9.3	—	8.6	—
C_2(C7–C8)/°	—	5.3	—	4.8	—	10.8
Puckering parameters						
q_2/Å	0.2544	0.5018	0.3391	0.2782	0.1458	0.4997
Φ/°	276	265	283	262	295	260
θ/°	75	113	71	114	67	111
Conformation[b]	$^{N5}S_{C9a}$	$^{C9a}S_{N5}$	$^{N5}S_{C9a}$	$^{C9a}S_{N5}$	$^{N5}S_{C9a}$ + E_{C9a}	$^{C9a}S_{N5}$
	flattened		flattened			

[a] W. L. Duax, C. M. Weeks, and C. D. Rohrer, *Top. Stereochem.*, 1976, **2**, 271. [b] S: screw-boat, E: sofa.

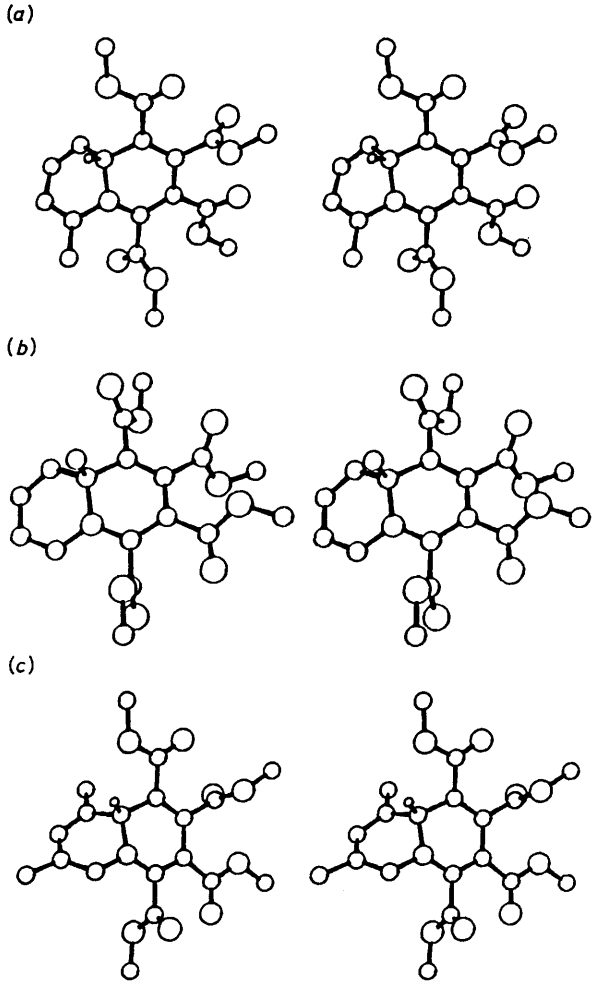


Figure 1. Stereopictures of (*a*) 6-methyl-1,2,3,4-tetracarboxylate-9a*H*-quinolizine (**2**); (*b*) 9a-methyl-1,2,3,4-tetracarboxylate-9a*H*-quinolizine (**6**); and (*c*) 7,9-dimethyl-1,2,3,4-tetracarboxylate-9a*H*-quinolizine (**12**).

part devoted to X-ray analysis). The ^{13}C NMR data are given in Tables 5–8. Table 5 gives the chemical shifts of the carbon atoms of (**1**) as δ values in the first row. For compounds (**2**)–(**17**), the results are given as shielding differences from (**1**). Table 6 contains shielding differences of the carbons of the ethyl-substituted compounds (**18**)–(**22**) from the corresponding carbons of (**1**). Table 7 presents the one-bond C–H coupling constants.

The system of labelling used for the carbon nuclei is explained in Figure 2. The carbon resonances can be divided into groups as follows: (*a*) the four resonances of the CO groups which have chemical shifts in the range 162–168 ppm, (*b*) the four resonances of the OCH_3 groups (50–55 ppm), (*c*) the resonances of the methyl and the ethyl substituents which lie between 7 and 30 ppm, (*d*) the sp^2-carbon resonances of rings A and B (90–150 ppm), and (*e*) the sp^3-carbon resonance of C9a which lies at *ca.* 60 ppm.

The carbon signals of ring A (C1–C4) could be easily distinguished from those of ring B (C6–C9) by the Overhauser effect. The latter were invariably more intense than those of ring A. This was true also for the methyl-substituted carbons. DEPT spectra, which were measured for all samples, confirmed the conclusions drawn from the Overhauser effects and also allowed one to distinguish between the methyl-substituted and unsubstituted carbons of ring B. This was particularly important in the case of closely positioned signals of similar intensity, such as those observed for C7 and C8 in compound (**7**). A significant aid in assigning the ring carbon nuclei was provided by the ^1H-coupled ^{13}C spectra with NOE retained using routine gated decoupling. These were recorded for all samples except (**11**), which isomerized too fast. The analysis of long-range coupling patterns provided easy assignment of the carbons C1–C4. C1 was observed in most compounds as a doublet of doublets; C2 and C4 were observed as doublets and C3 was always a singlet. The discrimination between C2 and C4 was rather straightforward since, owing to the electronegative effect of nitrogen, C4 appears invariably at lower field than any other carbon. Additional information was obtained from the analysis of the one-bond proton–carbon couplings. We have found that ^1J(6-H) > ^1J(9-H) ≥ ^1J(7-H) > ^1J(8-H) (see Table 7). Only in three cases do the assignments remain dubious. This concerns the following pairs of signals in which the assignments can be interchanged: C7 and C8 in (**9**), C6 and C9 in the same compound, and C8 and C9 in compound (**14**). However, the differences within each of the pairs are so small that reversal of the assignments does not influence our general conclusions.

The carbonyl ^{13}C resonances form a very characteristic pattern. The carbon of the carbonyl groups attached to C4 appears invariably at lowest field, *ca.* 167 ppm. The remaining three signals form a closely spaced group, within a range of 4 ppm, at *ca.* δ 164 ppm. Within the group, the signal at lowest field exhibits a coupling to H-9a in the ^1H-coupled spectrum for compounds (**4**), (**9**), (**12**), (**14**), (**20**), and (**21**). We therefore assign this signal to C=O at C1. Needless to say, all the signals also exhibit spin–spin coupling to the protons of the relevant OCH_3 moieties. The assignments for C=O at C1 in the remaining compounds were made by analogy with those listed above. For

Table 5. ^{13}C chemical shift (ppm) of tetramethyl 9a*H*-quinolizine-1,2,3,4-tetracarboxylate (**1**) and its monomethyl, dimethyl, and trimethyl derivatives (**2**)–(**17**).[a]

														CH_3 at				
	C1	C2	C3	C4	C6	C7	C8	C9	C9a	*C*O–C1	*C*O–C2	*C*O–C3	*C*O–C4	C6	C7	C8	C9	C9a
(1)[b]	113.77	135.44	97.57	148.28	126.16	113.23	121.29	120.30	54.68	163.95	163.72	163.10	167.26	—	—	—	—	—
(2)[b]	1.77	−1.68	−0.50	0.16	−9.26	−5.47	−0.84	−3.41	0.11	0.59	0.36	0.06	0.15	19.11	—	—	—	—
(3)	1.75	−0.98	2.03	−0.23	4.72	−11.24	−3.69	−1.03	0.12	0.00	−0.06	0.00	−0.16	—	15.28	—	—	—
(4)	−0.65	0.36	−0.06	0.20	0.55	−3.18	−8.69	4.63	−0.35	−0.23	−0.11	−0.14	−0.11	—	—	19.68	—	—
(5)[b]	5.90	−2.21	−0.81	0.68	2.76	−2.94	3.20	−10.21	−2.86	0.02	0.28	0.65	0.08	—	—	—	17.74	—
(6)[b]	−4.89	5.21	−2.45	2.22	0.66	6.45	0.80	−2.68	−5.41	−0.92	−0.09	−0.71	0.05	—	—	—	—	22.01
(7)	2.36	−2.66	0.77	−1.25	−3.49	−13.86	−5.90	−5.15	0.29	0.02	−0.02	−0.28	−0.34	16.44	16.61	—	—	—
(8)	1.01	−1.92	−0.79	−0.35	−8.97	−9.25	−9.84	0.95	−0.82	0.03	−0.10	−0.50	−0.34	19.08	—	19.35	—	—
(9)	3.21	−3.86	−0.81	−1.57	−8.66*,[c]	−7.26*	1.49*	−13.19*	−1.86	−0.55	0.04	−0.16	−0.31	19.03	—	—	17.25	—
(10)[b]	−9.45	8.18	−13.27	7.40	−9.80	8.12	0.66	−2.04	−5.87	−1.13	−0.72	−1.16	0.39	20.63	—	—	—	23.97
(11)	0.85	−0.73	2.66	−0.07	4.64	−13.45	−10.45	2.75	−0.21	−0.27	−0.11	−0.03	−0.30	—	16.21	17.80	—	—
(12)[b]	6.32	−3.10	0.59	−0.12	6.85	−14.15	−1.23	−11.20	−2.82	−0.35	−0.05	0.23	−0.28	—	17.93	—	17.50	—
(13)	−2.95	4.22	−1.17	2.08	5.17	−2.96	−2.87	−3.41	−5.06	−1.08	−0.40	−0.92	−0.20	—	17.89	—	—	22.05
(14)	4.98	−2.40	−1.27	0.72	2.94	−7.58	−3.30*	−3.19*	−3.74	−0.46	−0.24	0.16	−0.44	—	—	16.59	13.88	—
(15)[b]	−5.35	5.50	−2.51	2.50	1.32	3.11	−7.65	1.89	−5.63	−1.05	−0.21	−0.75	0.02	—	—	20.52	—	22.25
(16)	−2.92	6.57	5.32	5.66	1.84	6.52	2.76	−12.28	−8.69	−2.09	−0.44	−0.62	0.15	—	—	—	19.92	21.06
(17)	−10.07	8.15	−13.12	7.48	−9.18	4.50	−7.62	2.90	−6.08	−1.17	−0.71	−1.33	0.33	20.39	—	20.78	—	24.01
Z[d]	1.09	0.78	0.57	0.73	0.69	0.87	0.81	0.66	0.37	—	—	—	—	—	—	—	—	—

[a] For (**1**) the chemical shifts are given as δ values. For (**2**)–(**17**) the shifts are given as shielding differences relative to (**1**), apart from the 6-, 7-, 8-, 9-, and 9a-methyl shifts, which are given as δ values. [b] Results from ref. 6. [c] Assignments labelled with an asterisk are not fully established (see text). [d] *Z* = the standard deviations quoted at the bottom of the Table are concerned with the experimental shieldings computed from the fitted set of increments. The numbering system for the carbon nuclei is indicated in Figure 2.

Table 6. ^{13}C chemical shifts (ppm) of tetramethyl 9a*H*-quinolizine-1,2,3,4-tetracarboxylate (**1**) and its monoethyl derivatives (**18**)–(**22**).[a]

														CH_3CH_2 at				
	C1	C2	C3	C4	C6	C7	C8	C9	C9a	*C*O–C1	*C*O–C2	*C*O–C3	*C*O–C4	C6	C7	C8	C9	C9a
(1)	113.77	135.44	97.57	148.28	126.16	113.23	121.29	120.30	54.68	163.95	163.72	163.10	167.26	—	—	—	—	—
(18)	1.45	−2.54	−0.49	−0.82	−16.56	−5.17	−1.41	−5.11	−0.39	0.00	−0.02	−0.26	−0.32	26.65 13.41	—	—	—	—
(19)	1.45	−0.93	1.66	−0.41	5.36	−16.99	−2.71	−1.41	−0.14	−0.07	−0.05	−0.03	−0.07	—	25.48 13.18	—	—	—
(20)	−0.74	0.43	0.00	0.14	0.09	−0.88	−14.58	4.90	−0.38	−0.23	−0.04	−0.03	0.05	—	—	26.84 12.46	—	—
(21)	6.31	−2.61	−1.94	0.62	2.54	−2.71	5.15	−16.42	−3.13	−0.31	−0.14	0.30	−0.22	—	—	—	24.05 11.46	—
(22)	−4.87	5.26	−3.92	2.09	−1.05	7.13	−0.52	−1.66	−9.09	−0.83	−0.34	−0.78	−0.02	—	—	—	—	30.30 6.94

[a] For (**1**) the chemical shifts are given as δ values. For (**18**)–(**22**) the shifts are given as shielding differences relative to (**1**), apart from the 6-, 7-, 8-, 9-, and 9a-ethyl shifts, which are given as δ values. The numbering system for the carbon nuclei is indicated in Figure 2. [b] Results from reference 6.

Table 7. One-bond carbon–hydrogen coupling constants/Hz for tetramethyl 9a*H*-quinolizine-1,2,3,4-tetracarboxylate (**1**) and for its monomethyl- (**2**)–(**6**), dimethyl- (**7**)–(**16**), trimethyl- (**17**), and monoethyl- (**18**)–(**22**) derivatives.

		$^1J_{6\text{-H}}$	$^1J_{7\text{-H}}$	$^1J_{8\text{-H}}$	$^1J_{9\text{-H}}$	$^1J_{9a\text{-H}}$
(1)	9a*H*-Quinolizine[a]	183	169	166	171	—
(2)	6-Methyl-	—	169	167	171	147
(3)	7-Methyl-	178	—	160	168	149
(4)	8-Methyl-	183	167	—	169	149
(5)	9-Methyl[a]	184	166	163	—	147
(6)	9a-Methyl-	182	172	167	172	—
(7)	6,7-Dimethyl-	—	—	163	176	147
(8)	6,8-Dimethyl-	—	163	—	168	147
(9)	6,9-Dimethyl-	—	167	167	—	146
(10)	6,9a-Dimethyl[a]	—	168	165	172	—
(12)	7,9-Dimethyl[a]	182	—	161	—	147
(13)	7,9a-Dimethyl-	178	—	164	170	—
(14)	8,9-Dimethyl-	186	166	—	—	147
(15)	8,9a-Dimethyl-	176	165	—	165	—
(16)	9,9a-Dimethyl-	180	171	162	—	—
(17)	6,8,9a-Trimethyl-	—	167	—	167	—
(18)	6-Ethyl-	—	169	167	171	147
(19)	7-Ethyl-	186	—	165	173	148
(20)	8-Ethyl-	187	169	—	169	150
(21)	9-Ethyl-	188	167	167	—	148
(22)	9a-Ethyl-	179	170	168	174	—

[a] Results from ref. 6. The numbering system for the carbon nuclei is indicated in Figure 2.

the two remaining carbonyl resonances, *i.e.* those at C2 and C3, the assignments are tentative and can be reversed.

The ^{13}C chemical shifts of the ring carbons (C1–C4 as well as C6–C9a) for the parent compound (**1**) and for a set of its methyl-substituted derivatives (**2**)–(**17**) were fitted, by a least-squares procedure, to a simple additive scheme, representing the effects of the methyl substituents in all of the individual positions of the ring system. This was done independently for each of the ring carbons, in terms of the effects of methyl groups at positions C6–C9a, and the additional effect of two vicinal methyl groups (the vicinal effect) as well as that of two methyl groups simultaneously in positions C6 and C9a, which are likely to interact with the methoxycarbonyl substituents at ring A (the C6–C9a effect). The values of the increments obtained are presented in Table 8.

Discussion

The principal effect of methyl substitution in ^{13}C NMR spectroscopy is to cause a very large change in the shielding of the carbon at the position of substitution and of adjacent atoms. It can be interpreted in terms of the usual α and β effects. The α effects are typical of alkyl groups[15] and cause a deshielding of the affected sp^2 carbons by 8–10.5 ppm and about half as much for the sp^3 hybridized C9a (see Table 8). The β effect transmitted through a single bond, β^σ, causes a deshielding of adjacent sp^2 atoms by *ca.* 4 ppm, and by 2.7 ppm for sp^3 atoms. The absolute magnitude of the β effect transmitted through a double bond, β^π, falls within the same range (3.0–4.8 ppm) but its sign is reversed (except for 6-substituted compounds). The influence of methyl groups on the carbons in the γ position in ring B is negligible for substituents at C8 and ranges from *ca.* −3 ppm for the methyl group at C9 to −1.4 ppm for that at C7. Similar effects are also observed in ethyl-substituted compounds (**18**)–(**22**) (Table 6).

However, only in the case of CH_3 at C8 does the influence of the methyl group not reach further than that attributable to α and β effects (Table 8), *i.e.* C8, C7, and C9. The most remarkable difference between the 8-methyl group and methyl groups attached to C6, C7, and C9 concerns their effects on the shieldings of the carbons in ring A. The effect of substitution at C9 is revealed in a large shielding increase for C1 and a substantial deshielding for C2. The methyl group at C7 causes shielding of C1 and C3, and deshielding of C2 and C4. The methyl group at C6* does not influence C1 and only very slightly influences C3, and causes a deshielding of C2 and C4. The influence of the 9a-methyl substituent upon the shielding of the ring carbons is unusually large. It results not only in substantial deshielding of C9a (α effect) and of C1 and C9 (β^σ effect) but it causes additionally very large changes in the shielding of C2, C3, C4, and C7 (5.94, −3.38, 2.89, and 7.68 ppm, respectively). These changes are further enhanced by the introduction of a 6-methyl substituent into the 9a-methyl derivative. Thus, for example, the C6–C9a effect reaches −9.44 ppm for C3, and −4.69 ppm for C1 causing large deshielding by comparison with the corresponding monosubstituted 9a*H*-quinolizines. All remaining ring carbons, apart from C6, are strongly influenced by this effect. In order to obtain some insight into the origin of these rather unexpected effects we decided to carry out X-ray measurements for three typical compounds: 6-methyl- (**2**), 9a-methyl- (**6**), and 7,9-dimethyl-(**12**) 9a*H*-quinolizines. Though data obtained for crystals cannot be employed directly for the rationalization of results obtained in solution, we hoped that they would provide some information concerning the geometry of the compounds examined, which would help in the evaluation of the changes occurring in the ^{13}C NMR spectra of quinolizines.

The results of the X-ray analyses can be summarized as follows: (i) the C3–C4 bonds in all three compounds are considerably longer than the remaining three endocyclic double bonds and (ii) the C(1)–C(10) and C(3)–C(18) distances in compounds (**2**) and (**12**) are smaller than those between C(2)–C(14) and C(4)–C(22), respectively. The reverse order is observed for the C=O bonds, those at C1 and C3 being slightly longer than those at C2 and C4. In compound (**6**) only the C(3)–C(18) bond is clearly shorter than the three remaining C–CO bonds. The arrangement of the bonds at the nitrogen atom is always slightly pyramidal (see Table 4). In compounds (**2**) and (**12**), the CO_2Me groups attached to C1 and C3 are almost co-planar with the planes of the corresponding double

* An average for six compounds.

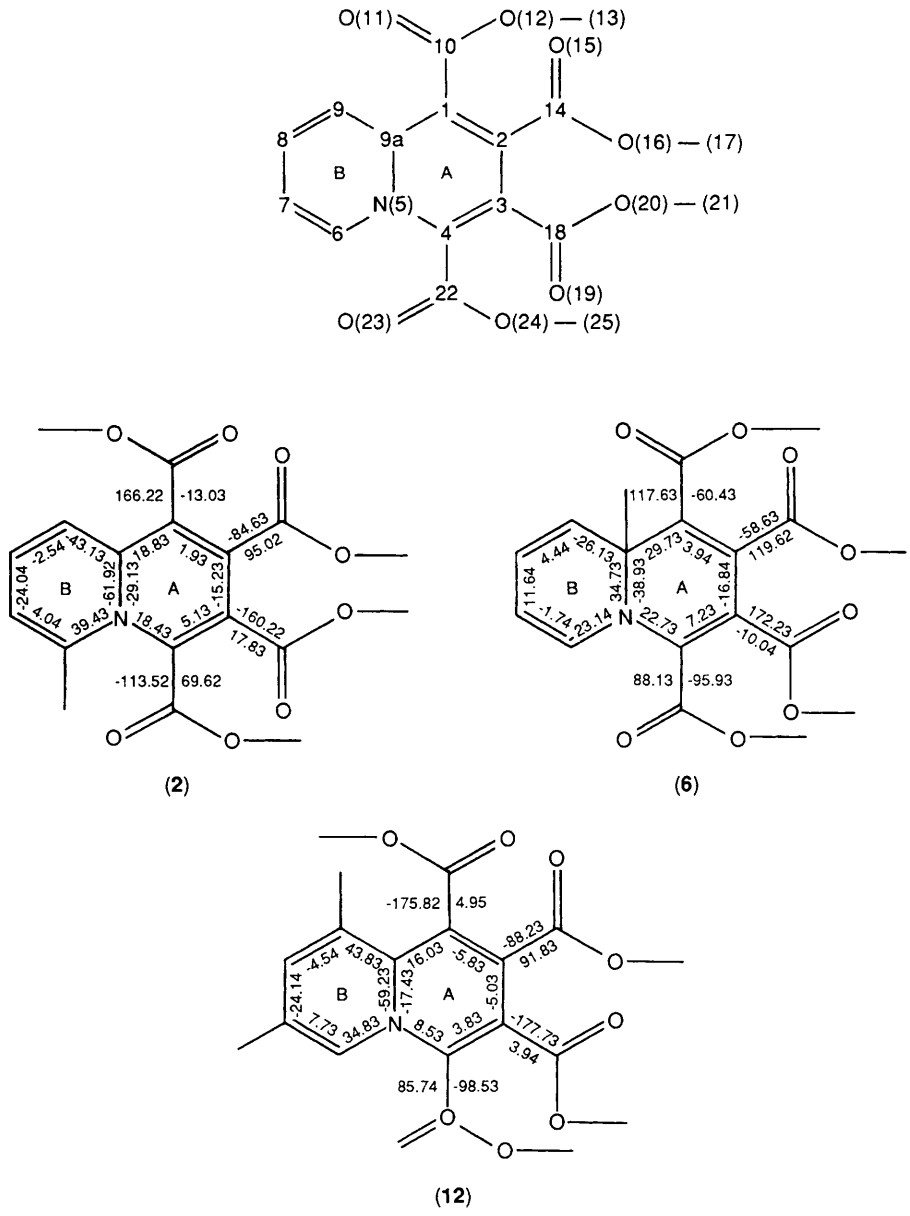


Figure 2. The numbering scheme and conformational details of (**2**), (**6**), and (**12**).

bonds, while the groups located at C2 are almost perpendicular to the plane of the C(1)–C(2) bond. Those at C4 are also strongly twisted away from the C(3)=C(4) plane (the corresponding torsion angles are given in Figure 2). In the 9a-methyl substituted compound (**6**) only the carbonyl group at C3 is co-planar with the double bond between carbons C3 and C4, while all of the remaining ester groups, including that at C1, are strongly twisted with respect to the planes of the relevant double bonds (see Figure 2).

Using the data collected in Table 1 and the Cremer–Pople method[16] we have also performed conformational analyses of rings A and B for the compounds examined. This shows that ring B exists in the expected $^{C9a}S_{N5}$ conformation in all three compounds (s-skew or 1,3-diplanar conformation). Ring A assumes conformation $^{N5}S_{C9a}$ in compounds (**2**) and (**6**) and presents a conformational hybrid of the $^{N5}S_{C9a}$ and E_{C9a} (envelope) forms in (**12**).

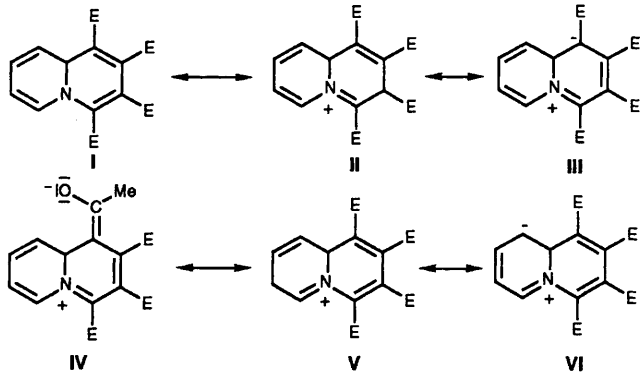
Thus, the main conclusion which can be drawn from the X-ray analysis concerns the stereochemistry of the O=C–C(1)=C(2) fragment. It became quite clear that only 9a-methyl substitution causes a very strong deviation of the carbonyl group attached to C1 from the plane of the double bond. In the 7,9-dimethyl substituted compound (**12**), on the other hand, the carbonyl group is co-planar with the C(1)–C(2) double bond. It is surprising that the coplanarity in (**12**) is retained in spite of apparently large steric hindrance between the 9-methyl group and the methoxycarbonyl group at C1. Evidence for the same situation in solutions follows from our ^{13}C NMR data for the carbonyl groups. As has already been pointed out (see *Results and Assignments*), the ^{13}C resonances of the carbonyl groups occur in a very narrow range, 162–168 ppm. The influence of methyl substitution at ring B on the carbonyl resonances is rather small for all four carbonyl groups in almost all compounds, including those substituted at C9. A substantial deshielding, however, of *ca.* 1 ppm is observed for the carbonyl carbons at C1 and C3 in all C9a alkyl substituted compounds [see results for (**6**), (**10**), (**13**), (**15**)–(**17**), and (**22**) in Tables 5 and 6]. These results are in accord with the X-ray data.

Table 8. The system of increments for carbon X upon substitution at carbon Y in methyl substituted tetramethyl 9a*H*-quinolizine-1,2,3,4-tetracarboxylates. The negative sign denotes deshielding of the carbons, positive denotes carbon shielding.

	X				
Y	C1	C2	C3	C4	C6
Z[b]	0.60 ± 0.74	0.00 ± 0.53	0.13 ± 0.39	0.08 ± 0.42	0.28 ± 0.47
6	0.29 ± 0.74	−1.86 ± 0.52	−0.60 ± 0.38	−1.32 ± 0.50	−9.60 ± 0.47
7	1.66 ± 0.71	−1.44 ± 0.51	1.99 ± 0.37	−0.78 ± 0.46	4.69 ± 0.45
8	−0.25 ± 0.65	−0.38 ± 0.47	0.26 ± 0.34	−0.11 ± 0.42	0.37 ± 0.41
9	3.95 ± 0.71	−1.87 ± 0.51	−1.14 ± 0.37	0.45 ± 0.45	1.65 ± 0.45
9a	−5.83 ± 0.74	6.05 ± 0.52	−3.13 ± 0.38	2.89 ± 0.46	0.24 ± 0.47
c	−0.58 ± 0.73	0.99 ± 0.52	−0.54 ± 0.38	1.01 ± 0.48	0.18 ± 0.46
d	−4.69 ± 1.22	4.16 ± 0.86	−9.72 ± 0.63	5.85 ± 0.82	−0.60 ± 0.77

	X				
Y	C7	C8	C9	C9a	*N*[a]
Z[b]	−0.30 ± 0.59	0.23 ± 0.55	−0.06 ± 0.45	−0.10 ± 0.25	17
6	−4.56 ± 0.59	−1.89 ± 0.55	−3.67 ± 0.45	0.32 ± 0.25	6
7	−10.53 ± 0.57	−3.88 ± 0.53	−1.44 ± 0.43	0.32 ± 0.24	5
8	−4.13 ± 0.52	−7.87 ± 0.48	4.83 ± 0.40	−0.42 ± 0.22	6
9	−2.97 ± 0.57	2.89 ± 0.53	−9.45 ± 0.43	−2.76 ± 0.24	5
9a	7.68 ± 0.59	0.14 ± 0.55	−2.59 ± 0.44	−5.31 ± 0.25	6
c	1.25 ± 0.58	0.42 ± 0.54	−0.19 ± 0.44	−0.32 ± 0.24	4
d	5.56 ± 0.96	1.97 ± 0.90	4.33 ± 0.73	−0.68 ± 0.41	2

[a] *N* is the number of equations in which the increments appear. [b] *Z* is the unsubstituted 9a*H*-quinolizine. [c] Vicinal effect—a correction for methyl groups in vicinal positions (6, 7 or 7, 8 *etc.*). [d] C6–C9a effect—a correction for the presence of two methyl groups simultaneously at positions C6 and C9a.



Scheme 3.

It can therefore be concluded that the substantial changes observed in the shielding of the carbons of rings A and B in compounds (**6**), (**10**), and (**17**) result not only from α, β, and γ effects, but also as a consequence of steric hindrance between the 9a-methyl substituent and the methoxycarbonyl group at C1. In particular, a large increase in the shielding of C7 is obviously caused by an increased contribution of resonance structure **V** at the expense of structure **IV** (see Scheme 3). Since steric hindrance cannot be invoked in the case of the remaining substituents, including those at C6 and C9, one has to interpret the observed large shielding of C1 in 9-methyl substituted quinolizines in terms of electronic effects. There are two effects which are important from this point of view. The first is the γ effect, which is known to be positive when transmitted *via* two single bonds. Its magnitude > 1 ppm.[15] The other is concerned with the hyperconjugation of the methyl group, which should cause an increase in the negative charge at C9, thus counteracting the conjugation of the lone pair of nitrogen with the π electron system of ring B. This in turn augments the conjugation of the lone pair with the π electrons of ring A. In other words, the contribution of the resonance structures **II** and **III** increases at the expense of structures **V** and **VI**, leading to an increase in the negative charge at C1 and C3. This conclusion is supported by the observation of the increased shielding of C1, effected by 7-methyl substitution, while such substitutions at C6 and/or C8 do not result in any significant effects. Needless to say, the effect of the methyl group at C7 cannot invoke any steric effects.

Finally, it is also interesting to notice that the signals of methyl substituents in ring B also follow a very characteristic pattern. The methyl group attached to C9a absorbs at lower field than any other methyl substituent and appears at 22.0 ppm in the mono-substituted compound (**6**), and at a similar position in (**10**), (**13**), and (**15**)–(**17**). The signals of the methyl groups bound to C6 and C8 are closely spaced, and appear at *ca.* 19 ppm in the mono-substituted compounds (**2**) and (**4**), and in the disubstituted compounds (**8**) and (**9**), while those belonging to the methyl groups at C7 and C9 occur at higher fields [15.28 ppm in (**3**), and *ca.* 18 ppm in (**5**), (**9**), (**12**), and (**13**)]. These observations are in good agreement with the predicted lower electron densities at positions C6 and C8, and larger densities at C7 and C9 (Scheme 3). Deviations from this pattern occur only for compounds in which the methyl groups are attached to two vicinal carbons *i.e.* compounds (**7**), (**14**), and (**16**).

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