A Mainly ^{13}C Nuclear Magnetic Resonance Investigation of Some Indolo[2,3-*a*]quinolizinylium Salts

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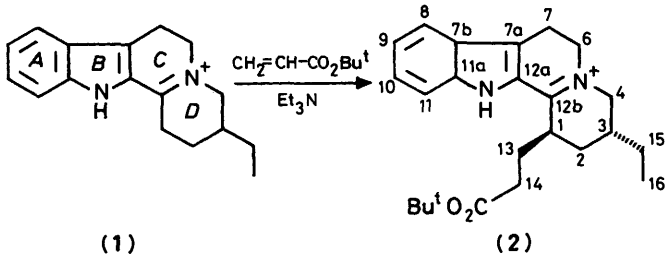
Several indolo[2,3-*a*]quinolizinylium derivatives have been studied by ^{1}H and ^{13}C n.m.r. spectroscopy. Two-dimensional carbon–proton correlation measurements and selective deuteriations have allowed complete ^{13}C assignment. Some stereochemical conclusions have been drawn.

Indolo[2,3-*a*]quinolizinylium salts are important intermediates in the synthesis of many indole alkaloids and related compounds.[1] In some cases the stereochemistry of these intermediates appears crucial to the outcome of their reactions.[2] However, in contrast to the widely examined indolo[2,3-*a*]quinolizine base analogues, to date no ^{13}C and very few ^{1}H n.m.r. data[3] on these iminium salts are available.

Recently these substances have often required detailed structure invstigation during our work in this field. We have reported[2] that in the course of the synthesis of tacamine, the intermediate (**2**) is formed in a highly diastereoselective manner (Scheme 1; only one enantiomer is depicted throughout).

With the aim of finding an explanation of this behaviour, we studied the stereochemistry of compound (**2**) by n.m.r. methods. In connection with these investigations it was necessary to have reliable ^{1}H and ^{13}C assignments. Therefore several indolo-[2,3-*a*]quinolizinylium derivatives (**1**)—(**7**) and analogues (**8**)—(**10**) (Scheme 2) were studied to support both signal assignments and stereochemical considerations.

In this paper definitive ^{13}C assigments and ^{1}H n.m.r. interpretations are presented for a few indolo[2,3-*a*]quinolizinylium salts, together with some stereochemical conclusions. The results served as useful aids during the preparation of tacamine[2] and in similar synthetic work to be published later.



(1) (2)

Scheme 1.

Results

Both ^{1}H and ^{13}C n.m.r. spectra of the iminium salts (**1**)—(**7**) show significant differences from those of the corresponding saturated bases, represented here by compounds (**8**)—(**10**). For the latter derivatives the assignments of the ^{13}C signals with $(CD_3)_2SO$ as solvent, but also in $CDCl_3$ solution for (**10**),‡ were mainly based on data reported for on (**9**)[4] and (**10**)[5] in $CDCl_3$. For (**8**), the C-12b and C-6 signals were identified by 2D (two-dimensional) ^{13}C–^{1}H correlation[6] measurements. For (**10**), although at 100 MHz the aliphatic ^{1}H region was very crowded, among the relatively closely spaced C-13, C-3, and C-7 signals that due to C-7 could be assigned from a ^{13}C–^{1}H correlation map, utilizing the fact that the 7-protons resonate to low field of those at positions 13 and 3. Also, the ^{13}C n.m.r. spectrum of a 1:1 mixture of (**10**) and its 1,12b-dideuteriated derivative showed doubling of the C-13 and C-2 signals ($\Delta\delta$ *ca.* 0.1 p.p.m.) due to deuterium isotope shifts,[7] thus proving the assignment of C-13. In view of this, previous assignments of C-13 and C-3 for (**10**)[5] are to be interchanged.

At 100 MHz the ^{1}H spectra of (**1**)—(**6**) exhibit very strongly coupled subspectra for the (angular) ring *D* protons, together with some inconvenient overlappings. Despite these difficulties the ^{1}H spectra were relatively easily interpretable by simple $^{1}H\{^{1}H\}$ decouplings and a 2D COSY-45 ^{1}H–^{1}H correlation map[8] for compound (**4**). The characteristic ^{1}H chemical shifts for (**1**)—(**8**) are listed in Table 1.

Most of the ^{13}C signals were unambiguously assigned from simple ^{13}C–^{1}H correlation maps measured for all compounds except (**5**). In compounds (**4**) and (**3**), however, the strongly coupled 2- and 3-protons are almost isochronous, a difficulty which is expected to arise even at very high fields, as the 400 MHz ^{1}H spectrum of (**4**) (Figure 1) demonstrates. Therefore the assignments of C-2 and C-3 in these compounds needed further investigations. Owing to the overlapping of the 2- and 15-proton signals, the identification of the corresponding carbon signals had to be supported by other methods as in the case of (**1**). For (**3**) and (**4**) the corresponding 1-deuteriated compounds were used to prove the assignment of C-2: a 0.1 p.p.m. isotope shift was observed with the non-deuteriated derivatives as internal standards in a 1:1 molar ratio. In the case of (**1**), C-2 and C-15 were easily assigned by applying simple substituent-induced chemical-shift (SCS) data for an equatorial ethyl group on cyclohexane.[9] In the case of (**2**), the C-1 and C-3 signals were unambiguously identified by the disappearance of the former from the ^{13}C spectrum of the corresponding 1-deuteriated compound. This reinforced the result of the 2D ^{13}C–^{1}H correlation experiment: the δ(H-1) > δ(H-3) relation showed that the signal at δ 35.7 corresponds to C-1, and at δ 28.4 to C-3.

In the case of the aromatic tertiary carbon atoms the assignment of C-11 is obvious from the upfield γ-effect of the NMe group on this signal[10] in compound (**5**) and from the small

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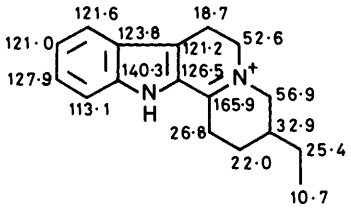
‡ Differences between the corresponding ^{13}C chemical shifts in the two solvents were within a few tenths of a p.p.m., and the relative positions of the closely spaced signals did not change.



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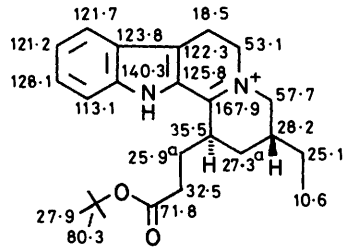

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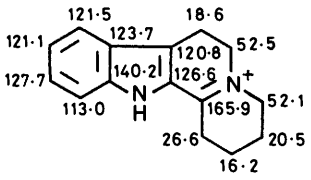

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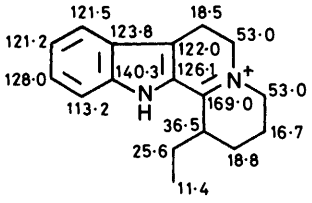

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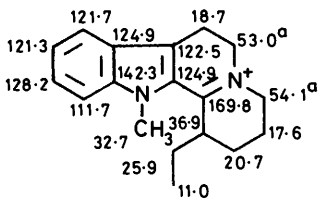

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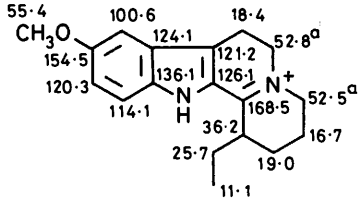

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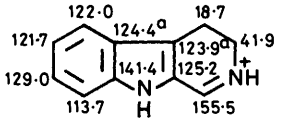

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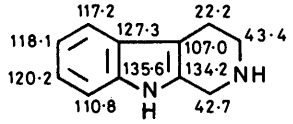

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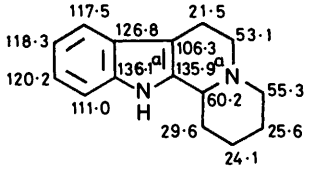

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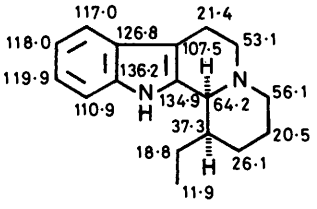


(10)

[a] Tentative assignment.

Scheme 2. ^{13}C Chemical shifts measured in $(CD_3)_2SO$ at 25.0 MHz; compounds (1)—(7) were all studied as perchlorate salts.

meta SCS value of the 9-OMe group[11] in (**6**). With knowledge of both ^1H–^1H and ^{13}C–^1H correlations, the assignments of the aromatic ^{13}CH and ^1H signals are well defined. [The aromatic CH signals were assigned on the same basis as for (**7**).]

Quaternary carbon signals were assigned by applying a combination of two methods. Additions of an excess of 1:1 H_2O/D_2O[12] to the solutions of compounds (**4**) and (**7**) caused doubling of the ^{13}C signals near 140 and 126 p.p.m. (C-11a and C-12a) ($\Delta\delta$ *ca.* 0.1 p.p.m.), while others were not affected. A COLOC (correlation *via* long-range couplings)[13] spectrum optimized for ^{13}C–^1H couplings of 6 Hz was also measured for (**4**), revealing the long-range couplings of the quaternary carbon atoms (Figure 1 and Table 2) and thus providing safe assignments.

By the use of the foregoing techniques, the assignments of the ^{13}C spectra of the investigated indoloquinolizinylium salts are well established.

Discussion

Chemical Shifts.—In comparison with the analogous saturated bases, the majority of the aliphatic ^{13}C signals of the investigated iminium salts show upfield shifts [*cf.* (**9**) with (**3**), and (**10**) with (**4**)]. The observed shifts can be attributed to both ring-flattening and inductive effects. For (**3**), a comparison with calculated chemical shifts derived from *trans*-decalin, 1,2,3,4,5,6,7,8-octahydronaphthalene,[14] linear amines,[9] and iminium salts[15] shows acceptable correlations only for C-4, C-3, C-6, and C-7. We note the huge upfield shifts of the C-2 signals ($\Delta\delta$ *ca.* -7 p.p.m.) in the γ-position with respect to N-5. In (**4**), however, the similarly γ-positioned C-13 shows a 6.8 p.p.m. downfield shift from its value in (**10**). In (**10**), the C-13 ethyl group occupies a predominant axial position[5,16] and, as it will later be shown, this is also true for compound (**4**). The downfield shift of C-13 in (**4**) can thus be attributed to the loss of a γ-*gauche* interaction with N-5.

Table 1. Characteristic ^1H chemical shifts for (1)—(8) measured in $(CD_3)_2SO$ at 100 MHz

	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)
H-1	3.25	3.53	3.20	3.37	3.70	3.30		
H-2	1.48	1.40—2.40	1.94	1.96	1.96	1.93		
H-3	2.00	1.40—2.40	1.94	1.96	1.96	1.93		
H-4	3.93(*e*) 3.54(*a*)	4.00(*e*) 3.54(*a*)	3.86	3.90	3.90	3.86		
H-6	4.09	4.05	4.07	4.05	4.05	4.03	3.85	2.97
H-7	3.28	3.28	3.27	3.00—3.40	3.00—3.40	3.00—3.40	3.60	2.56
H-8	7.73	7.76	7.76	7.78	7.78	7.15	7.58	7.33
H-9	7.18	7.20	7.21	7.20	7.23		7.07	6.90
H-10	7.41	7.45	7.46	7.48	7.52	7.10	7.35	6.97
H-11	7.53	7.54	7.57	7.60	7.70	7.46	7.49	7.25
H-12b							8.80	3.85
H-13		1.40—2.40		1.70	1.56	1.69		
H-14		1.40—2.40		1.06	0.98	1.02		
H-15	1.43	1.40—2.40						
H-16	1.09	0.96						

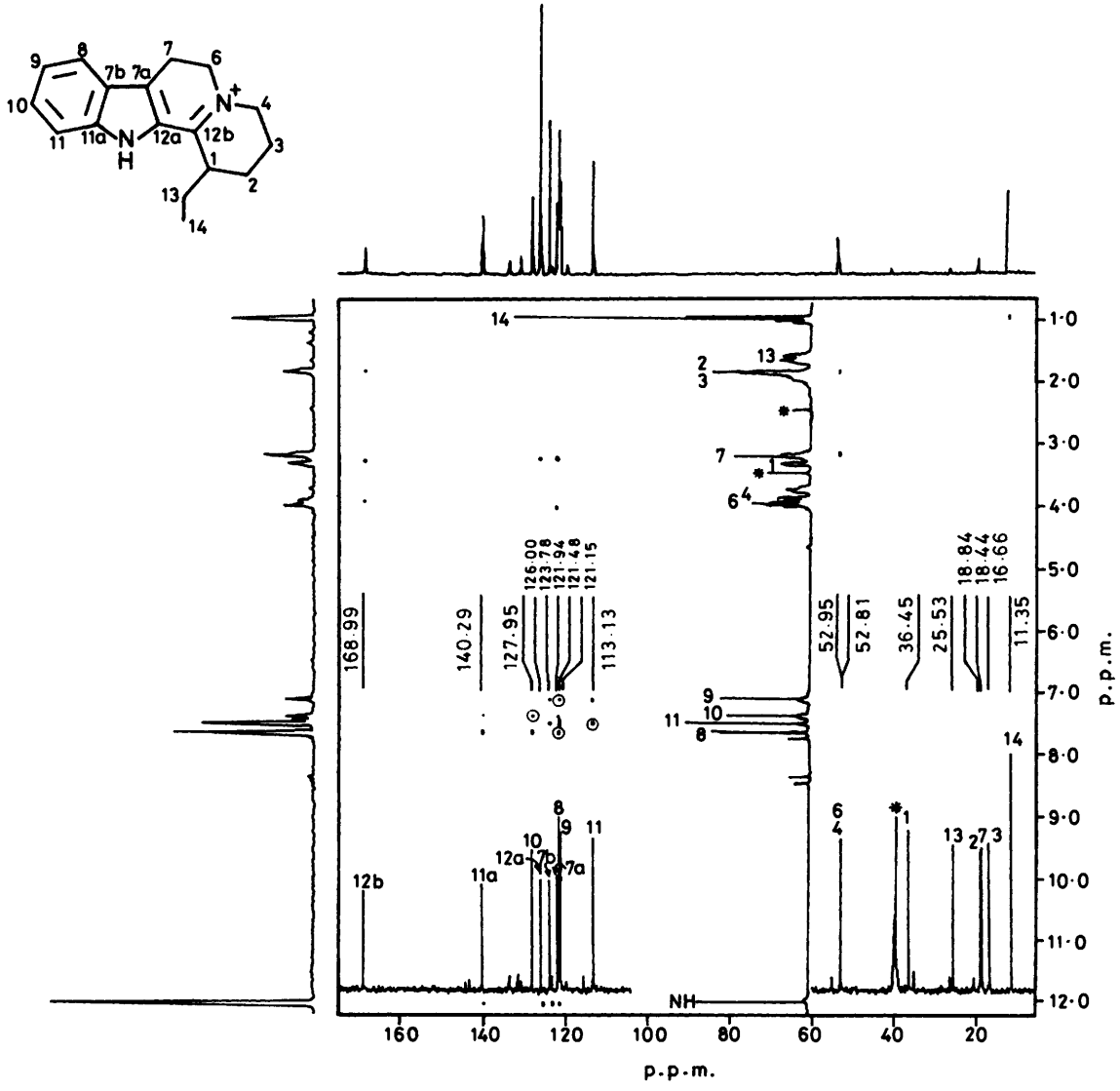


Figure 1. The COLOC (correlations *via* long-range coupling) spectrum of (4) measured at 9.4 T, optimized to 6 Hz ^{13}C–^1H couplings. For clarity, inside the map the broad-band ^1H-decoupled ^{13}C spectrum (horizontal) and the normal ^1H spectrum (vertical) are also depicted. Encircled peaks are due to one-bond ^{13}C–^1H couplings. Solvent peak is marked with an asterisk

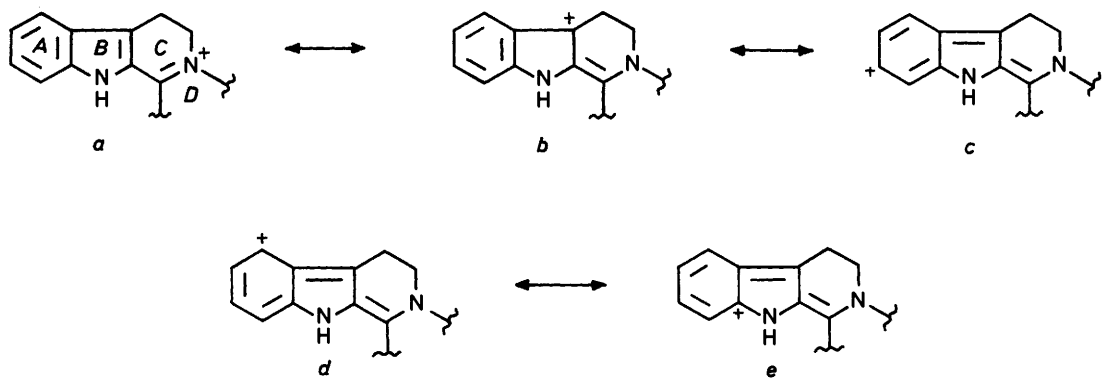


Figure 2. Canonical structures for the β-carbolinylium unit

Table 2. Observed ^{13}C–^{1}H long-range correlations for compound (4) as shown in Figure 2

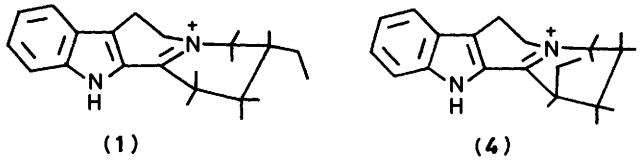
	^{2}J	^{3}J
C-12a	NH	H-7
C-12b	H-1	H-6, H-2
C-6	H-7	
C-7a	H-7	H-6, NH
C-7b		H-9, H-11, NH
C-8		H-10
C-9		H-11
C-10		H-8
C-11		H-9
C-11a	NH	H-10, H-8
C-4		H-2

Most of the aromatic ^{13}C signals of the iminium salts show considerable downfield shifts, mainly for C-7a (Δδ *ca.* +15 p.p.m.), C-8 (+4.5 p.p.m.), C-10 (+8 p.p.m.), and C-11a (+4 p.p.m.). Qualitatively, these shifts are easily understood in terms of the canonical structures illustrated in Figure 2.

In addition to the principal contribution of form *a*, the pronounced deshielding effect on C-7a points to the greater importance of form *b* over *c*, *d*, and *e*, due to its intact π-electron sextet in ring *A*. The reason for the higher downfield shift for C-10 than for C-8 and C-11a might be the *para*-quinonoid electronic distribution in structure *c*. The upfield shifts (−9 p.p.m.) of the C-12a signals can be understood in terms of the enamine structures in canonical forms *b*, *c*, *d*, and *e*.

In connection with these considerations it is interesting that, as recent experiments have revealed, the regioselectivity of aromatic electrophilic substitutions on indolo[2,3-*a*]quinolizinylium derivatives is different from that of compounds containing the unit (**8**). For example in the former case ring *A* can be brominated in position 9 (position 11 is sterically unfavourable), while in the latter case bromination occurs in positions 8 and 10.[17] This behaviour of the iminium salts arises from a reversed alternation of the frontier electronic distributions in ring *A* as compared with compounds containing the simple indole chromophore. The same tendency is found in the alteration of ground-state electronic densities in these iminium salts, as reflected by the strong downfield shifts of C-8, C-10, and C-11a.

It is also of interest to examine the differences between the *ortho* methoxy SCS values for compound (**6**) [Δδ(C-8) *ca.* −20.9, Δδ(C-10) *ca.* −7.7 p.p.m.]. Such asymmetric *ortho* effects for the OMe (and OH) group have been reported in aromatic systems, including different types of indole chromophores.[11] As compared with the latter, this asymmetry (according to the present data) is even more apparent in indoloquinolizinylium salts. The phenomenon is usually related to the



(1) (4)

Figure 3. The predominant conformations of (**1**) and (**4**)

mesomeric effect of the OMe group, which polarizes the *ortho*-carbon atoms differently.[18] An expected preference for one of the two coplanar methoxy conformations (affecting the *ortho*-positions sterically) should also be considered. Such conformational preferences of the OMe group in similar systems are well documented,[19] although to our knowledge no reasonable explanation has yet been found for this behaviour. However, by considering the difference in charge densities of the *ortho* carbon atoms, which might arise partly from the mesomeric effect already mentioned above, one can arrive at a plausible explanation if one assumes that the oxygen lone pairs are preferentially oriented towards the more positive *ortho*-carbon atom.

Stereochemistry.—On account of the complexity of the higher order subspectra of the ring *D* protons, stereochemical considerations were based on ^{13}C chemical shifts (Scheme 2). For ring *D*, the half-chair conformation is assumed throughout. Ring *C* inversion causes slight changes in the steric interactions between the C-1 substituent and the indolic portion. Ring *C* is considered to exist mainly in that conformation which accommodates these repulsions most favourably. In compound (**1**), the C-3 ethyl group is considered to assume a predominantly equatorial position. In (**4**), from the SCS values measured for C-1, C-2, and C-3 [*cf.* (**3**)] it can readily be concluded that the C-1 ethyl group is in a *quasi*-axial position (Figure 3). The small deviations from Et_{ax}(SCS) data[9] can be attributed either to the *quasi*-axial character of the substituent and/or to a non-negligible presence of the conformer containing a *quasi*-equatorial ethyl group. The latter possibility, however, can be regarded as more unlikely in view of the analogous SCS values found for compound (**5**). For (**5**), owing to the strong steric repulsion between the NMe group and an equatorial proton of C-13, the conformational equilibrium is expected to be forced towards the *quasi*-axial situation. The C-13 and ring *D* carbon signals in (**5**), however, are shifted only very slightly from their values in (**4**), indicating that the predominant conformation of (**4**) has not been changed by introducing the NMe group. This is in agreement with the stereochemistry found for compound (**10**), where a predominant axial C-1 ethyl group has been previously reported.[5,14]

The stereostructure of (**4**) also accounts for the stereoselective

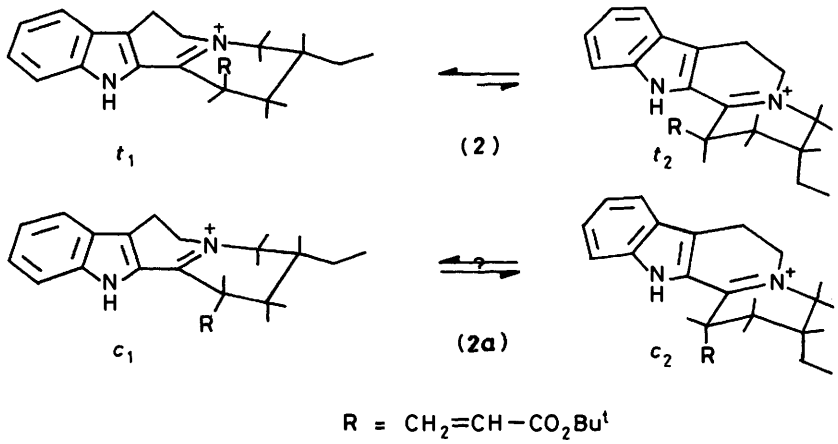


Figure 4. The most important conformations of (**2**) and its epimer (**2a**)

formation of (**10**) on reduction by either sodium borohydride or catalytic hydrogenation.[16] Under steric approach control the hydride anion or hydrogen attacks the less hindered side of the molecule, leading to isomer (**10**) with H-1 and H-12b in *cis* positions. This assumption might serve as a general explanation for the stereoselectivity of the reduction of similar 1-substituted indolo[2,3-*a*]quinolizinylium derivatives (see ref. 2 for previous communications in this series).

For compound (**2**), four theoretical stereostructures have to be considered (Figure 4). From model studies, none of the four structures can *a priori* be excluded. In view of the elucidated geometry of (**4**), however, structure t_1 seems to be the thermodynamically most stable form. (With c_2 a 1,3-diaxial arrangement is involved; t_2 and c_1 also appear rather unfavourable owing to the steric interactions associated with the *quasi*-equatorial substituent R, but the possibility of stabilization through an N_{ind}–H • • • O=C bridge may not be ignored.) The C-3 signal in (**2**) is −4.7 p.p.m. upfield of its position in (**1**), whereas the chemical shift of C-1 as compared with that in (**4**) is practically unchanged. Theoretically, these data are in accord with structures t_1, t_2, and c_2. For t_1 the effect on C-3 is due to the γ-*gauche* interaction with C-13; in c_2 and t_2 it may be attributed to the reduced α-SCS value of the *quasi*-axial ethyl group. Furthermore, in t_2 the upfield shift for C-1 arising from the γ-*gauche* effect from C-15 might possibly be counterbalanced by the downfield shift due to the *quasi*-equatorial C-1 substituent. The conformation c_2 represents a rather rare situation where, in terms of the most widely used theories,[20] the steric arrangement of the equatorial H-1 and C-15, as well as that of H-3 and C-13, might lead only to a very small upfield shift of C-1 and C-3 signals. Structure c_2, however, can easily be ruled out since the presence of an axial C-3 ethyl group would be unambiguously reflected through upfield shifts of the C-4 and C-2 signals relative to their values in (**1**). Analogously, the lack of upfield shifts on C-4 and C-15, as compared with (**1**), excludes the possibility of a predominant t_2 conformation. ^{13}C Data thus assign stereostructure t_1, the thermodynamically most favoured form, to compound (**2**). In view of this, the diastereoselectivity of the reaction in Scheme 1 is easily understood. The enamine formed from (**1**) on basification reacts with acrylic ester rather slowly; thus product development control can be assumed by applying the Hammond principle. Since (**2**) compares favourably with (**2a**) on steric grounds, this explains the stereoselective formation of the epimer (**2**).

Experimental

N.m.r. Measurements.—The ^1H and ^{13}C n.m.r. spectra were recorded in the pulsed Fourier transform mode (16 K data points for the field induction decay) at 99.54 and 25.00 MHz, respectively, with a JEOL FX-100 instrument. The ^1H and ^{13}C chemical shifts were determined with tetramethylsilane as internal standard. Carbon multiplicities were determined by the attached proton test (APT) method.[21] The concentration dependence of the ^{13}C chemical shifts for the iminium perchlorates in Me_2SO was negligible. Typical acquisition parameters for the two-dimensional ^{13}C–^1H correlation measurements were: spectral width 5000—1000 Hz, delay time 1 s, number of increments 100, FT size 1K × ½K.

The 2D COLOC spectrum for (**4**) was recorded with a Bruker AM-400 spectrometer, by use of the Bruker standard software: the parameter set was optimized to a ^{13}C–^1H coupling constant of 6 Hz.

Materials.—Compounds (**1**),[22] (**2**),[2] (**3**),[23] (**4**),[24] (**5**),[25] (**6**),[26] (**7**),[27] (**8**),[28], (**9**),[29] and (**10**)[16] were either routinely available, or prepared according to the reference given. The perchlorates (**9**) and (**12**) were obtained from the corresponding bases by standard methods.

Selective deuteriation at C-1 and C-12b in (**10**) was achieved by reduction of the corresponding enamine[24] with $NaBD_4$ in CD_3OD. Deuteriation at C-1 in the iminium salts (**2**)—(**4**) was carried out as follows: the corresponding enamine was acidified with CF_3CO_2D, and subsequently converted into the perchlorate salt with $Mg(ClO_4)_2$ in CD_3OD. As its ^1H n.m.r. spectrum revealed, in the enamine form of (**2**) the position of the double bond (1, 12b) is analogous to those of the enamines of (**4**)[23] and (**3**).[24]

Acknowledgements

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