N-Methylated Products of the *Solanum* Steroidal Alkaloids Tomatidine and Solasodine

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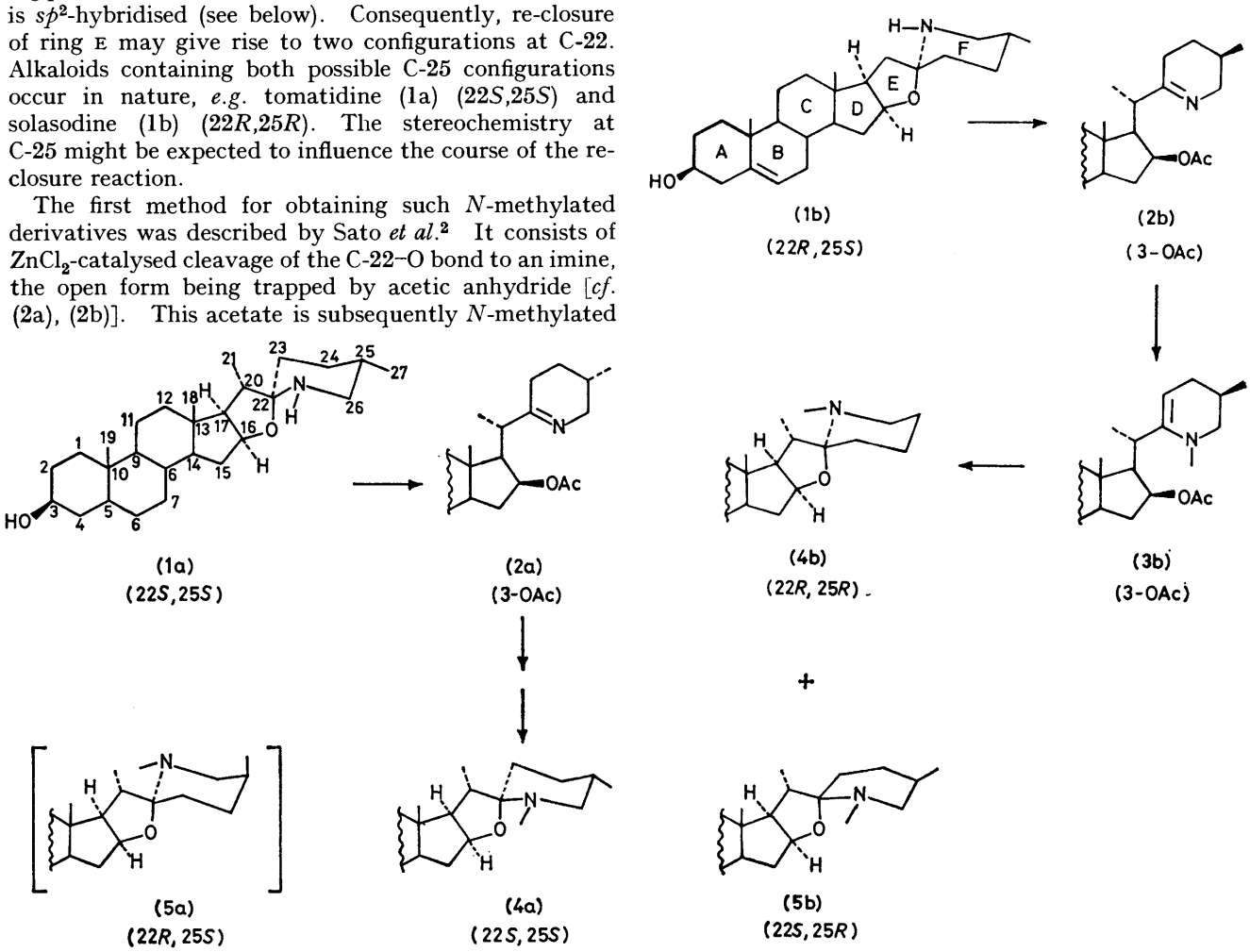
The *Solanum* steroidal alkaloids tomatidine and solasodine contain a spiro-ring junction with azaketal functionality. The conversion of the natural products to their *N*-methylated derivatives involves intermediates in which the formerly spiro-carbon (C-22) is sp^2 hybridized, and therefore the stereochemical information at this centre is lost. ^{13}C N.m.r. analysis is used to show that methylation of tomatidine (22*S*,25*S*) results in one (22*S*,25*S*) product, while the same treatment on solasodine (22*R*,25*R*) affords two isomers that can equilibrate in solution, with 22*R*,25*R* (major) and 22*S*,25*R* (minor) stereochemistry. The ^{13}C n.m.r.-derived conformations of the products suggest an explanation for these results.

DURING a study of microbial transformations of *N*-methylated derivatives of *Solanum* steroidal alkaloids,[1] it came to our attention that the configurations and the conformations of some of these derivatives were not unambiguously established. In particular, in the case of alkaloids containing a spiro-centre at C-22, all methylating procedures involve intermediates in which this carbon is sp^2-hybridised (see below). Consequently, re-closure of ring E may give rise to two configurations at C-22. Alkaloids containing both possible C-25 configurations occur in nature, *e.g.* tomatidine (1a) (22*S*,25*S*) and solasodine (1b) (22*R*,25*R*). The stereochemistry at C-25 might be expected to influence the course of the re-closure reaction.

The first method for obtaining such *N*-methylated derivatives was described by Sato *et al.*[2] It consists of $ZnCl_2$-catalysed cleavage of the C-22–O bond to an imine, the open form being trapped by acetic anhydride [*cf.* (2a), (2b)]. This acetate is subsequently *N*-methylated with MeI and re-closed by basic hydrolysis of the acetate moiety. When applied to tomatidine (1a), this procedure led to a single product.[2] A few years later, Uhle [3] prepared *N*-methylsolasodine by a different method, and isolated two isomeric compounds. Neither group of workers could prove unambiguously the stereochemistry of their products. Recently, Bird *et al.*[4] prepared *N*-



SCHEME Methylation of tomatidine and solasodine

methylsolasodine by Sato's method; one pure compound crystallised in high yield from the reaction mixture. ^{13}C N.m.r. analysis suggested this to be the 22*R*,25*R* isomer.

In view of the ambiguity of these results we decided to undertake a ^{13}C n.m.r. study of the course of *N*-methylation of tomatidine (1a) and solasodine (1b) by Sato's method. This task was made possible by our ^{13}C n.m.r. data of these starting materials.[5]

RESULTS

N-Methyltomatidine.—Tomatidine (1a) was converted to pseudotomatidine diacetate (2a) by the procedure of Sato *et al.*[2] The ^{13}C (see Table 1) and ^{1}H n.m.r. (see Experimental section) data are in agreement with the structure. This tetrahydropyridine derivative was transformed *via* its methiodide salt into *N*-methyltomatidine (4a).[2] Even the crude, uncrystallised product proved to be pure (>95%) by n.m.r.

The ^{13}C n.m.r. spectrum allows the assignment of this compound to the stereochemistry (4a). Thus, comparison of its chemical shifts (see Table 1) with those of tomatidine

TABLE 1

^{13}C N.m.r. data [a]

Carbon	(2a) [b]	(4a)	(2b) [b]	(3b) [b]	(4b)	(5b)
1	36.6	37.0	36.9	36.9	37.3	37.3
2	27.5	31.4	27.7	27.7	31.6	31.7
3	73.7	71.1	73.8	73.9	71.8	71.8
4	34.0	38.2	38.1	38.1	42.3	42.3
5	44.6	44.9	139.8	139.8	140.9	140.9
6	28.9	28.7	122.3	122.4	121.4	121.5
7	31.8	32.2 [c]	31.7	31.7	32.2	32.3
8	35.0	34.8	31.4	31.5	31.2	31.2
9	53.9	54.5	50.0	50.0	50.2	50.2
10	35.5	35.6	36.6	36.6	36.7	36.7
11	21.0	21.2	20.8	20.8	21.0	21.0
12	39.8	40.5	39.6	39.8	40.3	40.3
13	42.3	41.4	42.0	42.2	41.3	41.1
14	54.1	55.5	54.2	54.6	55.7	55.7
15	34.6	32.4 [c]	34.6	34.5	30.8 [c]	32.3
16	75.4	77.8	75.0	74.9	84.9	77.6
17	56.5	61.5	56.4	59.0	64.1	61.5
18	13.2	17.0	13.0	12.7	16.5	16.7
19	12.2	12.4	19.3	19.3	19.4	19.4
20	39.9	37.0	40.8	31.5	43.4	37.3
21	18.4	15.1	18.8	21.5	15.1	15.6
22	173.4	101.5	173.6	150.3	103.2	102.4
23	28.5 [c]	27.8 [d]	28.2 [c]	95.3	38.7	25.6 [c]
24	28.2 [c]	28.0 [d]	27.9 [c]	31.5	30.0 [c]	23.1 [c]
25	27.5	31.4	27.2	26.4	34.1	28.1
26	56.8	60.4	56.7	60.1	59.3	58.3
27	19.2	19.4	19.1	19.3	19.3	17.9
N-Me		34.8		39.5	41.0	34.7

[a] See Experimental section for details. [b] $\delta(MeCO_2)$ 21.3 ± 0.1 and 170.4 ± 0.2. [c,d] Signals with the same superscript within any vertical column may be interchanged.

(1a) [5] shows only minor differences. Carbons 21, 23, 24, 25, and 27 are virtually unchanged, indicating the equatorial conformation of C-27. On the other hand, the N-Me appears at very high field (34.8 *vs.* 46.5 p.p.m. in *N*-methylpiperidine [6]), and C-20 is shielded by 5.8 p.p.m. relative to (1a),[5] indicating a γ-interaction [7] and therefore a *cis* relationship between N-Me and H-20. Since the latter is β-oriented, the 22-configuration of tomatidine is conserved, as shown in (4a).

N-Methylsolasodine.—*N*-Methylsolasodine was prepared from solasodine (1b) by the method of Sato *et al.*[2] Thus, (1b) was converted into pseudosolasodine diacetate (2b), which afforded (3b). Both these compounds proved to be homogeneous by n.m.r. (see Table 1 and Experimental section), as expected [the chemical shifts of the ring D and side-chain carbons of (2b) and the tomatidine-derived related compound (2a) are very similar, but not identical, since they have opposite C-25 configurations]. Closure of ring E led to *N*-methylsolasodine. ^{13}C N.m.r. analysis of the crude product revealed it to be a mixture of two isomers [(4b) and (5b)] in a *ca.* 60 : 40 ratio. From a solution of this material in acetone, crystals were obtained whose ^{13}C n.m.r. spectrum indicated them to be the pure (>95%) minor isomer (5b). Its melting point (174—179 °C) agrees fully with one of Uhle's products (175—179 °C). On standing in deuteriochloroform for 2 days, partial equilibration (presumably through O-protonation and cleavage of the C-22–O bond to an intermediate where the C-22 stereochemistry is lost) led to a mixture containing *ca.* 25% of (4b). The mother-liquors of the crystallisation, however, contained (4b) and (5b) in the same ratio (60 : 40) as the crude. These results indicate a reversible isomerisation on standing in solution, rather than the existence of a metastable isomer, as suggested by Uhle.[3] As reported by Bird *et al.*, crystallisation from methanol leads to pure (4b).[4]

^{13}C N.m.r. analysis allows the identification of the major and minor constituents of the equilibrium mixture as (4b) and (5b), respectively. Thus, for (4b), the C-27 shift is virtually identical to the corresponding carbon in (1a), (1b),[5] and (4a), showing that this methyl group is equatorial. The C-20 absorption is also unchanged relative to (1a) and (1b),[5] indicating no γ-effect [7] on this carbon, as was the case for (4a). The N-Me group must therefore point away from H-20 to the α side of the molecule, feeling no γ-effect from C-20 and appearing at 6.4 p.p.m. to lower field than in (4a). This configuration is confirmed by the major (*ca.* +7 p.p.m.) shift of C-16 relative to (1a), (1b),[5] and (4a), due to the loss of a γ-effect, which is transmitted through H-16α and a C-23 hydrogen [for (1a) and (4a)] or the N-hydrogen or lone pair [for (1b)]. *N*-Methylation eliminates this interaction.

In the spectrum of (5b), however, the C-16 shift is back at its ' normal ' position at δ *ca.* 78, and the *N*-methyl absorption is at high field; therefore the C-22 configuration is opposite to that of solasodine (1b) and the major isomer (4b), with the nitrogen atom towards the β-side of the molecule, as in tomatidine (1a) and its derivative (4a). But due to the 25*R* configuration of (5b), C-27 cannot remain equatorial. Indeed, its chemical shift, which had remained fixed at δ 19.3 ± 0.1 in all the compounds with a C-22 spirocentre presented so far, changes to δ 17.9. This difference is smaller than the expected *ca.* 5 p.p.m. shielding in going to an axial methyl group, and the conformation of ring F

TABLE 2

^{1}H N.m.r. data [a]

Proton	(4a)	(4b)	(5b)	Multiplicity [b]
6		5.34	5.34	m ($W_{\frac{1}{2}}$ 10 Hz)
16	4.08	4.63	4.12	dt (8.5, 7)
3	3.58	3.52	3.52	tt (10, 5)
26-eq	2.58	<2.45	2.95	dd (11, 4)
N-Me	2.40	2.37	2.37	s (3 H)
21	0.91	1.11	0.95	d (3 H) (7)
27	0.85	0.87	1.08	d (3 H) (6.5)
18	0.84	0.80	0.87	s (3 H)
19	0.83	1.03	1.03	s (3 H)

[a] See Experimental section for details. [b] Coupling constants (*J*/Hz) in parentheses.

for (5b) is probably a twist-boat similar to the one shown on the formula, expressed also in high-field shifts for all the carbons in this ring relative to the 25-epimer (4a).

The ^{1}H n.m.r. data for the *N*-methylated compounds (Table 2) are in agreement with these structural assignments. Thus, the 27-Me signal, at δ 0.86 ± 0.01 when the group is equatorial [(4a), (4b), and (1b) [4]] is deshielded to δ 1.08 in (5b) (twist-boat ring F). On the other hand, both the H-16 and H-21 signals are deshielded in (4b) [relative to (4a), (5b), and (1b) [4]] by the interaction of these protons with the *N*-methyl group on the α-side of the molecule.

DISCUSSION

The course of the ring-E re-closure reaction towards the *N*-methylated alkaloids as shown above (either during the basic hydrolysis of the acetate or in a subsequent equilibration step), can be explained by taking into account the steric interactions around ring F. In all the compounds examined, the C-22–O bond is axial to this ring, while the C-22–C-20 bond is equatorial, a consequence of the much greater steric bulk of the methyl-substituted C-20 as compared to an oxygen atom.*

If C-20 remains equatorial, the re-closure reaction in the solasodine (25*R*) system must follow one of two courses: (*i*) retention of configuration (to 22*R*) leading to an interaction of the '*syn*-axial' type (like the one between two 1,3-diaxial substituents in a cyclohexane ring) between the *N*-methyl and C-21; or (*ii*) inversion of configuration (to 22*S*) leading to axial C-27, or loss of the chair conformation for ring F. Both possibilities carry energetically unfavourable, but unavoidable, features. The experimental results show that course (*i*) is slightly preferred (by *ca.* 1 kJ mol^{-1}).

In the case of tomatidine (25*S*), again two outcomes are possible: (*i*) retention (to 22*S*), in which case none of the two interactions described in the previous paragraph exists; or (*ii*) inversion (to 22*R*), when both interactions would exist. Clearly, now, the re-closure would be expected to follow course (*i*), and indeed the product of course (*ii*) is not observed (thus the energy difference is >7 kJ mol^{-1}).

EXPERIMENTAL

The n.m.r. spectra were recorded on Bruker WH-270 (^{1}H) and WH-90 (at 22.63 MHz, ^{13}C) spectrometers, operating in the Fourier-transform mode. All chemical shifts given in Tables 1 and 2 are in p.p.m. downfield from internal $SiMe_4$, for solutions in $CDCl_3$. The ^{13}C signals observed in noise-decoupled spectra were assigned by comparison to the reported data for tomatidine (1a) and solasodine (1b); [5] by analysis of single-frequency off-resonance decoupled (sford) spectra to obtain multiplicity and residual couplings (and therefore a correlation with the ^{1}H spectrum); and *via* inversion-recovery experiments that allow differentiation of carbon types through their relaxation times.

N-*Methyltomatidine* (4a).—This compound was prepared from tomatidine according to Sato *et al.*,[2] involving an acid-catalysed opening of ring E to give pseudotomatidine diacetate (2a); δ 5.16 (td, *J* 8, 4 Hz; H-16), 4.68 (tt, *J* 10, 5 Hz; H-3), 3.68 (dd, *J* 17, 4 Hz; H-26-eq), 2.90 (dd, *J* 17, 10 Hz; H-26-ax), 2.49 (dq, *J* 11, 7 Hz; H-20), 2.01 and 1.97 (s, each 3 H, 2 × $MeCO_2$), 1.08 (d, 3 H, *J* 7 Hz, 21-Me), 0.88 (d, 3 H, *J* 6.5 Hz, 27-Me), 0.85 (s, 3 H, 18-Me), and 0.82 (s, 3 H, 19-Me); ^{13}C n.m.r., see Table 1. Compound (2a) was methylated and re-closed to yield *N*-methyltomatidine (4a), m.p. 216—217 °C (for spectral data see Tables 1 and 2).

N-*Methylsolasodine* (4b) *and* (5b).—Solasodine was treated with $ZnCl_2$–Ac_2O in acetic acid by the method of Sato *et al.*[2] to give pseudosolasodine diacetate (2b); δ 5.36 (br d, *J* 4.5 Hz, H-6), 5.21 (td, *J* 8, 4 Hz, H-16), 4.68 (m, H-3), 3.62 (dd, *J* 17, 4 Hz, H-26-eq), 2.97 (dd, *J* 17, 10 Hz, H-26-ax), 2.03 and 2.00 (s, each 3 H, 2 × $MeCO_2$), 1.10 (d, 3 H, *J* 7 Hz, 21-Me), 1.03 (s, 3 H, 19-Me), 0.89 (s, 3 H, 18-Me), and 0.85 (d, 3 H, *J* 6.5 Hz, 27-Me).

Compound (2b) was converted into the methodide which upon reaction with potassium hydroxide solution [2,4] afforded *N*-methylsolasodine. The crude product contained two isomers in a *ca.* 60 : 40 ratio. Recrystallization from acetone yielded small white crystals, m.p. 174—179 °C (see text).

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* One of the referees has brought to our attention that a nitrogen analogue of the anomeric effect would also favour an axial oxygen substituent and could contribute to the observed constancy of the axial orientation of the C22–O bond.

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