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NMR Studies and the Absolute Configuration of *Solanum* Alkaloids (Spiroaminoketal Alkaloids)

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Nuclear magnetic resonance spectra of spiroaminoketal alkaloids from the plant genus *Solanum* have been used to study the side chain stereochemistry. The known absolute configuration at C-25 of the alkaloids together with the equatorial conformation of the C-27 methyl group as obtained from the spectra allow the assignment of the configuration at C-22. Tomatidine is then (22*S*:25*S*)-5α-spirosolanol-(3β) (I) and 5α-solasodanol-(3β) (22*R*:25*R*)-5α-spirosolanol-(3β) (III). For comparison reasons the NMR spectra of some steroidal sapogenins have been studied. These spectra are consistent with structures previously proposed.

The stereochemistry of the nucleus in the spiroaminoketal alkaloids found in the plant genus *Solanum* has for the most part been well delineated.[1,2] However, the stereochemistry of the spiroaminoketal side chain is much less well known. The asymmetric centers at C-22 and C-25 permit the existence of a maximum of four side chain diastereoisomers assuming that all known spiroaminoketal alkaloids have the same configuration at the other asymmetric centers. Only two of the four possible isomers are known. They can be represented by 5α-tomatidanol-(3β) (= tomatidine) and 5α-solasodanol-(3β) or by the unsaturated derivatives Δ^5-tomatidenol-(3β) and Δ^5-solasodenol-(3β) (= solasodine); all four are naturally occurring.

The close relationship between the spiroaminoketal alkaloids and the steroid sapogenins has been established by Uhle and Moore [3] by synthesis of tomatidine from pseudoneotigogenin, just as Uhle [4-6] transformed kryptogenin and pseudodiosgenin into solasodine. Furthermore, the schools of Briggs and Sato [7,8] have synthesized neotigogenin and diosgenin from tomatidine

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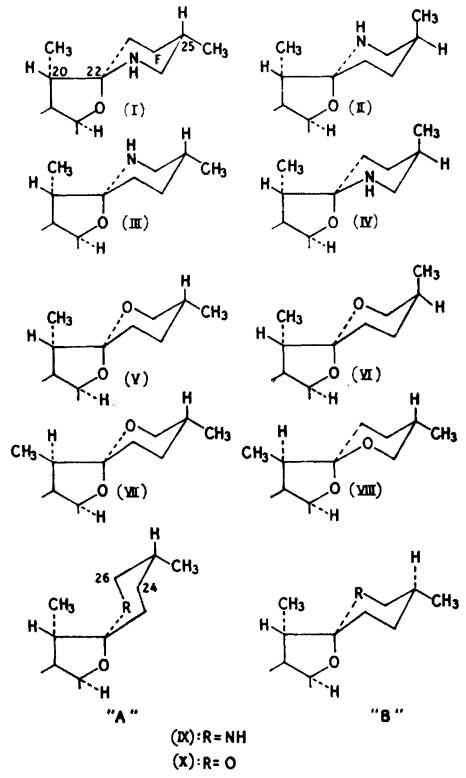
and solasodine, respectively. These transformations clearly indicate that tomatidine is a 25*S* (or 25 β_F) compound and 5α-solasodanol-(3β) a 25*R* (or 25 α_F) compound. The same results were obtained by Schreiber [9,10] who related the configuration at C-25 to (*S*)-α-methylglutaric acid for tomatidine and to (*R*)-α-methylglutaric acid and (*R*)-4-amino-3-methylbutyric acid for 5α-solasodanol-(3β). No chemical evidence is available for determining the configuration at C-22, but various chemical and physical properties seem to indicate that the two series also differ at C-22.[9,11–13]



Tomatidine can, therefore, be represented by the structures (I) or (II) and 5α-solasodanol-(3β) by the structures (III) or (IV).

In order to get further data which might prove the stereochemical relationships we have examined the nuclear magnetic resonance spectra of Δ^5-tomatidenol-(3β), tomatidine (I), solasodine and 5α-solasodanol-(3β) (III) and for comparison reasons the NMR spectra of diosgenin (V), sarsasapogenin (VI), cyclopseudodiosgenin (VII), and cyclopseudosarsasapogenin (VIII). It should be mentioned that the NMR spectra of the latter four compounds have earlier been recorded and discussed in terms of the spiroketal side chain.[14,15]

Table 1.

Substance	C-19	C-18	C-21	C-27	C-3	C-6 (vinyl)	C-16	C-26
Δ^5-Tomatidenol-(3β)	1.03	0.84	0.97	0.85	3.48	5.33	4.13	2.74
Tomatidine (I)	0.83	0.83	0.97	0.85	3.53	—	4.13	2.73
Solasodine	1.02	0.82	0.94	0.85	3.50	5.34	4.28	2.62
5α-Solasodanol-(3β) (III)	0.79	0.83	0.93	0.84	3.59	—	4.26	2.63
Diosgenin (V)	1.03	0.81	0.97	0.80	~ 3.5	5.34	4.40	~ 3.4
Sarsasapogenin acetate (VI)	0.99	0.77	1.09	1.00	5.1 (acetate) 4.1 (alcohol)	—	~ 4.4	3.30 } 3.98 }
Cyclopseudodiosgenin (VII)	0.97;	1.02	1.15	0.80	~ 3.5	5.35	4.46	~ 3.5
Cyclopseudosarsasapogenin (VIII)	0.98;	1.02	1.10	0.80	4.15	—	~ 4.5	~ 3.5

All values are δ [ppm] relative to TMS = 0

By referring to Table 1 it can be seen that the δ-value for the C-27 methyl group is constant throughout the two alkaloid series and the iso sapogenins examined contrary to the examined neosapogenin, sarsasapogenin, indicating that the conformation at C-25 is identical in the three series of compounds provided that the conformation of ring F does not change. Although there are two chair conformations of ring F one of them is much less probable because of steric interference of the C-21 methyl group with the 26-methylene group (IX, X) (conformation "A") or with the 24-methylene group, if the alkaloid has a 22-β-N configuration. Hence the other possibility (conformation "B") with the C-22-*O*-C-16 bond in an axial position has to be considered for the following analysis.

In the present study the increased magnetic field (23.4 kilogauss, 100 Mc) as compared to previous sapogenin studies of Rosen, Ziegler, Shabica and Shoolery, [14] and Kutney [15] allowed to completely resolve the doublets of both secondary methyl groups at C-20 and C-25 besides the singlets of the angular methyl groups (C-18, C-19). The chemical shifts (0.84—0.85 ppm) found for the C-27 methyl protons in the *Solanum* alkaloids are in very good agreement with the values already published and now confirmed for equatorial methyl groups at C-25 in sapogenins (near 0.8 ppm). It has been found that — other things being equal — *axial* methyl groups at C-25 always appear at lower field (higher δ) with typical $(\Delta\delta)_{ax,\ equat.} \approx 0.2$ ppm. The replacement of the ring oxygen atom by a nitrogen atom in the alkaloids is not expected to invalidate this rule.

The above found C-27 methyl resonance held together with the known absolute configuration at C-25 makes it necessary to conclude that the two alkaloid series have to differ in configuration not only at C-25, but also at C-22, but leaves the problem to decide which alkaloid has the 22-α-N and which one the 22-β-N-configuration. By referring to evidence for sapogenins of the neo- and iso-series being *S*- and *R*-epimers, respectively, but possessing the same 22-α-*O* configuration (*cf.* Ref. 16) * it is indicated that the C-27 methyl groups of the two alkaloid series both possess an equatorial conformation. Therefore, with the aforementioned assumption concerning the conformation of ring F being correct, we believe that it is possible to conclude that the absolute configuration for the two series of spiroaminoketal alkaloids is established. Tomatidine being a 25 *S* compound must with the C-27 methyl group placed in an equatorial position of necessity have the nitrogen atom situated above the plane of the nucleus (22-β-N) and can be named (22*S*:25*S*)-5α-spirosolanol-(3β) (I).** The C-27 methyl group of 5α-solasodanol-(3β) placed as above will cause the compound to have the nitrogen atom placed below the plane of the nucleus (22-α-N), the name will then be (22*R*:25*R*)-5α-spirosolanol-(3β) (III).

* Although it is admittedly questionable to compare conformations in the crystal with such in solution, it should be mentioned that X-ray data [17,18] have been in agreement with the assignment of an equatorial C-27 methyl group of the two iso sapogenins diosgenin and tigogenin.

** The nomenclature here used is based on the proposal by Schreiber [9,19] that the spiroaminoketal alkaloids are named spirosolans in analogy with the spirostan nomenclature for spiroketal sapogenins.

From the significant although very small difference in the chemical shifts of the C-16 proton resonance as well as the C-20 methyl resonance it can be substantiated that the two series of alkaloids in fact are C-22 enantiomers. The C-16 proton resonance is found at 4.13 ppm in the tomatidan series, whereas it shifts to 4.26 — 4.28 ppm in the solasodan series.

That the two alkaloid series do not differ in configuration at C-20 is confirmed, particularly since a 20-α_F-configuration should be indicated by a low field shift of the C-18 methyl group as found in the spectra of cyclopseudodiosgenin and cyclopseudosarsasapogenin.

In the spectrum of sarsasapogenin there is a large difference in the shifts of the two methylene protons at C-26 ($\sim$ 0.7 ppm). At the same time the C-27 methyl resonance is shifted to lower field by 0.2 ppm compared to all the other compounds. The above cited authors[14,15] have explained these findings with an axial conformation of the C-27 methyl group in this sapogenin as in neotigogenin. In the 100 Mc spectrum of sarsasapogenin and the acetate we have found that the signal of the protons at C-26 consists of a quartet ($\delta_{AB} \approx 0.6$ ppm, $J = 11$ c/s) in which the lowfield doublet is further split into a quartet with $J \approx 2.5$ c/s, whereas the high-field doublet is broadened to a similar extent. The absence of a strong coupling ($J_{ax,\,ax} > 7$ c/s) of one of these methylene protons with the C-25 proton gives strong support for an equatorial conformation of this proton and hence an *axial* methyl group at C-25 in sarsasapogenin although conformational changes of ring F might also be considered to explain the large chemical shifts of the C-26 protons.

In relation to the above discussion it should be mentioned that our assignment of structures to the sapogenins as given in the table is in complete agreement with the work of Rosen, Ziegler, Shabica and Shoolery,[14] and Kutney.[15] Further, the chemical shift of the C-3 proton (4.1 ppm) in sarsasapogenin is too low for an axial hydrogen, which in diosgenin and cyclopseudodiosgenin as well as in the alkaloids appears at 3.5 ppm. This result together with the fact that the signals at 4.1 ppm in sarsasapogenin and at 4.15 ppm at cyclopseudosarsasapogenin have a much smaller width, *e.g.* the protons lack the two "diaxial" neighbours at C-2 and C-4, definitely indicates that each of the two 5β-sarsasapogenins has an equatorial proton and hence an axial hydroxyl group, confirming the assignment of a 3β-hydroxyl group.

EXPERIMENTAL

Proton spectra were measured with a VARIAN HR-100 (Mc) spectrometer in $CDCl_3$ solution with tetramethylsilane as internal standard. Calibration was obtained by the usual sideband technique or from spectra measured on an A-60 (Mc) instrument. The chemical shifts are expected to be accurate to ± 0.01 ppm for the methyl resonances and ± 0.03 ppm for other protons.

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REFERENCES

1. Prelog, V. and Jeger, O. In Manske, R. H. F. *The Alkaloids*, Academic Press, New York 1960, Vol. VII, p. 343.
2. Boit, H.-G. *Ergebnisse der Alkaloid-Chemie bis 1960*, Akademie Verlag, Berlin 1961, p.758.
3. Uhle, F. C. and Moore, J. A. *J. Am. Chem. Soc.* **76** (1954) 6412.
4. Uhle, F. C. *J. Am. Chem. Soc.* **75** (1953) 2280.
5. Uhle, F.C. *J. Am. Chem. Soc.* **76** (1954) 4245.
6. Uhle, F. C. *J. Org. Chem.* **27** (1962) 656.
7. Briggs, L. H. and O'Shea, T. *J. Chem. Soc.* **1952** 1654.
8. Sato, Y., Latham, Jr., H. G., Briggs, L. H. and Seelye, R. N. *J. Am. Chem. Soc.* **79** (1957) 6089.
9. Schreiber, K. *Abhandl. Deut. Akad. Wiss. Berlin, Kl. Chem. Geol. Biol.* **1957** 143.
10. Schreiber, K. *Chem. Ber.* **98** (1965) 323.
11. Toldy, L. *Acta Chim. Acad. Sci. Hung.* **16** (1958) 403.
12. Boll, P. M. *Acta Chem. Scand.* **14** (1960) 783.
13. Boll, P. M. and Sjöberg, B. *Acta Chem. Scand.* **17** (1963) 1176.
14. Rosen, W. E., Ziegler, J. B., Shabica, A. C. and Shoolery, J. N. *J. Am. Chem. Soc.* **81** (1959) 1687.
15. Kutney, J. P. *Steroids* **2** (1963) 225.
16. Shoppee, C. W. *Chemistry of the Steroids*, Butterworths, London 1964, p. 398.
17. Kennard, O. *Intern. Union of Crystallography, Sixth Intern. Congress and Symposia*, Rome 1963, Abstracts of Communications A 49.
18. O'Donnel, E. A. and Ladd, M. F. C. *Chem. Ind. (London)* **1963** 1984.
19. Schreiber, K. *Z. Chem.* **3** (1963) 346.

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