134. (5*R**,9*S**)- and (5*R**,9*R**)-2,2,9-Trimethyl-1,6-dioxaspiro[4.4]non-3-ene and their Dihydro Derivatives as New Constituents of Geranium Oil

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Summary

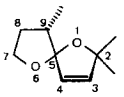
(5*R**,9*S**)- and (5*R**,9*R**)-2,2,9-Trimethyl-1,6-dioxaspiro[4.4]non-3-ene (**1a** and **1b** resp.) and their dihydro derivatives **2a** and **2b** are described as new constituents of geranium oil. The structures and configurations of **1a**, **1b**, **2a**, and **2b** are based on spectra interpretation and syntheses. Also some other monoterpenoid constituents identified in the same boiling range are discussed.

Introduction. – One of the most important essential oils in perfumery is certainly geranium oil. It is obtained by steam distillation of the leaves and branches of *Pelargonium graveolens* and other species of *Pelargonium* [1–3]. The high interest in this perfumery raw material of various geographic origins is very well reflected by over hundred papers dealing with its chemical composition [2–22]. Up to now, *ca.* 120 components have been identified which represent over 95% of the total oil. Taking advantage of the considerable progress achieved in instrumental methods since our analysis performed in the early sixties, we reinvestigated a commercial Reunion geranium oil by the usual methods of isolation (distillation, CC and GLC) and identification (IR, NMR, GLC/MS including comparison with authentic samples).

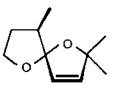
Among more than 270 constituents identified mainly by GLC/MS, the new bicyclic acetals **1a**/**1b** and **2a**/**2b** attracted special attention from a structural point of view. They will be the main subject of this paper.

The separation of the low boiling fraction of Reunion geranium oil (b.p. 30–76°C/12 Torr, 3.2% of the total oil) by CC (silica gel, hexane/Et_2O 10:1) led to fractions containing about 20% of two unknown isomeric constituents of mol. wt. 168 ($C_{10}H_{16}O_2$ according to high resolution mass analysis) in a ratio of 7:3. The major isomer **1a** showing the shorter retention time could be isolated by prep. GLC in a purity of 94%, whereas the minor isomer **1b** was only 87% pure (accompanied by 10% of **1a** and 3% of an unknown constituent). These two isomers having a minty, fresh, herbaceous odor represent together *ca.* 0.005% of the total oil. Based on the spectral data (IR, NMR, MS), the structures of the spiroacetals **1a** and **1b** could be proposed. Neither **1a** nor **1b** show an optical rotation.

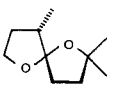
In slightly less polar fractions of the same CC (hexane/Et_2O 10:1), also the corresponding dihydro derivatives **2a** and **2b** (7:3, 0.001% of the total oil) could be local-



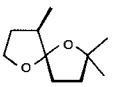
1a



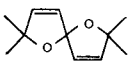
1b



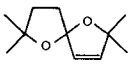
2a



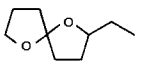
2b



A



B



C

ized by GLC/MS and finally be isolated in small quantities (2 and 1 mg, resp.). The isomer **2a** proved to be identical with the hydrogenation product of **1a** and **2b** with that of **1b**.

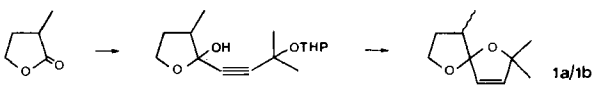
During the last 30 years, several natural products containing the 1,6-dioxaspiro[4.4]nonane unit have been described. *Bohlmann et al.* [23] identified various alkadiynylidene-substituted spiroacetal enol ether in *Chrysanthemum* spp., and *Graf & Dahlke* [24] assigned the structure of the 7-ethyl-1,6-dioxaspiro[4.4]nonane-2-acetic acid to the so-called 'Exogonsäure' isolated by *Mannich & Schumann* [25] from *Ipomoea operculata*. Later on, *Naya & Kotake* [26] isolated the 2,2,7,7-tetramethyl-1,6-dioxaspiro[4.4]nona-3,8-diene (**A**) and its dihydro derivative **B** from hop oil. Finally, the discovery of the so-called 'chalcogran' (**C**) in the aggregation pheromone of the *'Kupferstecher'* beetle (*Pityogenes chalcographus* L.) by *Francke et al.* [27] brought increasing attention to this class of bicyclic acetals. Among these 1,6-dioxaspirononanes, **1a**/**1b** and **2a**/**2b** are the first examples which follow the isoprene rule.

Structure Elucidations and Syntheses. – The mass spectra (M^+ at *m/z* 168 and 170, resp.) and the ^{1}H-NMR spectra (16 and 18 protons, resp.) indicated the empirical formula $C_{10}H_{16}O_2$ for **1a**/**1b** and $C_{10}H_{18}O_2$ **2a**/**2b**. The typical O-containing mass fragments $M^+ - 45$ (for **1a**/**1b** *m/z* 123, $C_8H_{11}O$; for **2a**/**2b** *m/z* 125, $C_8H_{13}O$) and $M^+ - 55$ (for **1a**/**1b** *m/z* 113, $C_6H_9O_2$; for **2a**/**2b** *m/z* 115, $C_6H_{11}O_2$) together with the existing knowledge concerning the mass fragmentation of 1,6-dioxaspiro[4.4]nonanes gave a first hint at such structures.

All ^{1}H-NMR data (see *Exper. Part*) for these spiroacetals were compatible with the structures **1a**/**1b** and **2a**/**2b**, resp. The configuration of CH_3–C(9) in **1a** and **1b** could be elucidated by nuclear-*Overhauser*-effect (NOE) experiments. In the case of **1b**, irradiation of CH_3–C(9) resulted in a NOE of 20% for H–C(4). The analogous experiment in the case of **1a** did not influence the signal for H–C(4).

To verify the structures and to evaluate the olfactive properties, **1a**/**1b** were synthesized following the procedure described for **B** [28] by reaction of the lithium salt of 2-methyl-3-butyn-2-yl tetrahydropyranyl ether with an equimolar amount of α-methyl-γ-butyrolactone, subsequent hydrogenation (*Lindlar* catalysts) and acid-catalyzed de-

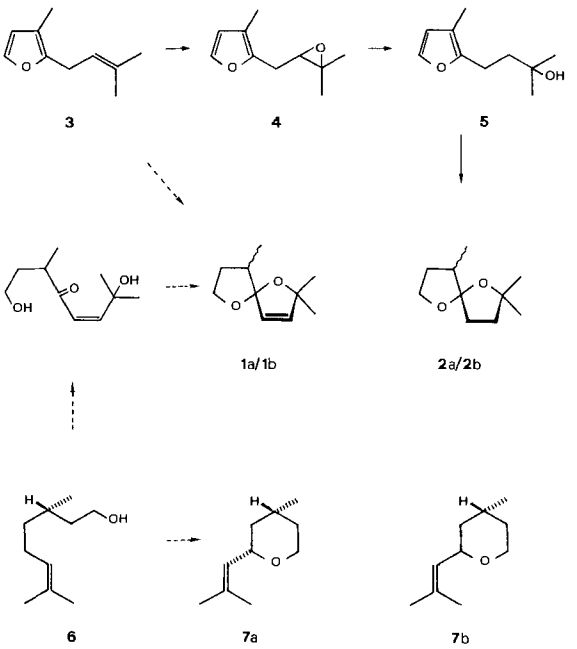
Scheme 1



protection/cyclization *(Scheme 1)*. Hydrogenation of **1a** and **1b** finally led to the dihydro derivatives **2a** and **2b**, resp.

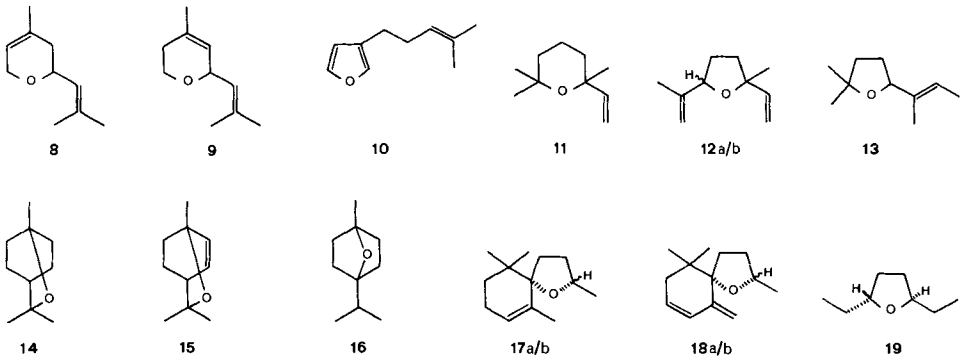
An independent synthesis for **2a**/**2b** was effected based on the knowledge that β-(2-furyl)alkanols cyclize to 1,6-dioxaspiro[4.4]nonanes on hydrogenation [29] [30]. For this purpose, rose furan (**3**) was epoxidized to **4**. Reductive opening of the oxirane ring in **4** with $LiAlH_4$ led to the tertiary alcohol **5**, which was hydrogenated/cyclized (MeOH, Pd) in 50% yield to a 7:3 mixture of **2a**/**2b** *(Scheme 2)*.

Scheme 2



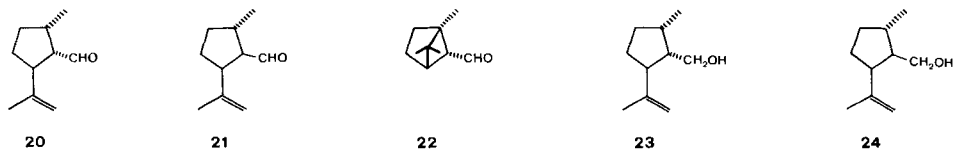
Since rose furan (**3**) together with its epoxide **4** also occurs in geranium oil (0.01% and 0.005%, resp.), **1a**/**1b** and subsequently **2a**/**2b** might be formed *via* **3** as intermediate. On the other hand, it seems conceivable that **1a**/**1b** are formed on an analogous biogenetic route as the diastereoisomers of (−)-rose oxide (**7a**/**7b**, 1.1% of geranium oil) from (−)-citronellol (**6**) [31]) by photooxygenation, allylic oxidation, and subsequent cyclization.

Further Trace Constituents. – The investigation of the low-boiling fraction of Reunion geranium oil by CC and GLC/MS also allowed the identification of a series of known natural monoterpenoid ethers, such as nerol oxide (**8**; 0.02%) and its double bond isomer **9** (trace), perillene (**10**; trace), 2,2,6-trimethyl-6-vinyltetrahydropyran (**11**; 0.15%) [10], the *cis*- and *trans*-deoxy ether of linalool oxide (**12a**/**b**; 0.1%), the 2,2-dimethyl-5-(1′-methyl-1′-propenyl)tetrahydrofuran (**13**; trace), 1,8-cineol (**14**; 0.03%), 1,8-epoxy-*p*-menth-2-ene (**15**; trace) [32], 1,4-cineol (**16**; trace), the diastereoisomeric theaspirans (**17a**/**b**; trace) and vitispirans (**18a**/**b**; trace) [33] and the (−)-*trans*-2,5-diethyltetrahydrofuran (**19**; 0.1%) [34].



Like nerol oxide from Bulgarian rose oil [35], our specimen **8** showed no optical rotation.

A further example demonstrating the importance of photochemical reactions in the formation of geranium trace constituents is given by the occurrence of the photocitral isomers **20**, **21**, and **22** (6:3:1; together 0.04% *versus* 1% for the two isomers of citral) which have been identified by us several years ago as important constituents of verbena oil [36].



GLC/MS also allowed the identification of the corresponding alcohols **23** and **24** as trace constituents.

Helpful discussions with Drs. *E. Billeter, J. Schmid, G. Fràter, D. Lamparsky* and *U. Huber* are kindly acknowledged.

Experimental Part

(With the valuable collaboration of Mr. *E. Stocker* and Mr. *R. Thoma*)

General Remarks. See [37].

Isolation of 1a–2b from Geranium Oil. – Distillation of 5113 g of commercial Reunion geranium oil through a 45-cm *Widmer* column gave a fraction of 161.5 g (3.2%, b.p. 30–76°/12 Torr) consisting of α-pinene, **11**, 3-methylpentyl formate, α-phellandrene, myrcene, **12a/b**, limonene, β-phellandrene, 3-methylcyclohexanone, *cis*- and *trans*-ocimene, *p*-cymene, methyl 3-methylcyclopentyl ketone, 3-methylpentan-1-ol, 6-methyl-5-hepten-2-one, terpinolene, 1-hexanol, *cis*-3-hexen-1-ol, *trans*-2-hexen-1-ol, **7a/b**, methyl 3-methylcyclopentenyl ketone, **10**, *cis*- and *trans*-linalool oxide, 1-octen-3-ol, menthone, isomenthone, linalool, and numerous minor and trace constituents. CC of this fraction (4000 g of silica gel) with hexane/Et_2O 10:1 led to subfractions containing **1a/1b** to about 20% in a ratio of 7:3. Prep. GLC allowed to isolate **1a** and **1b** in purities of 94 and 87%, resp. From slightly less polar fractions of the same CC (also hexane/Et_2O 10:1), the corresponding dihydro isomers **2a** and **2b** could be isolated in purities of *ca.* 90%.

Hydrogenation of **1a** *and* **1b**. The spiroacetal **1a** (7 mg) in 3 ml of hexane was hydrogenated in the presence of 2 mg of Pd/C. Usual workup gave 4 mg of **2a** (purity *ca.* 90%). The analogous experiment with 5 mg of **1b** resulted in 3 mg of **2b** (purity *ca.* 90%).

Spectral Data of **1a–2b**. *(5R*,9S*)-2,2,9-Trimethyl-1,6-dioxaspiro[4.4]non-3-ene* (**1a**). IR: 1269, 1190, 1172, 1148, 1120, 1070, 1015, 990, 947, 882, 850, 805. ^{1}H-NMR (400 MHz): 0.98 (*d*, *J* = 6.5, CH_3–C(9)); 1.29, 1.39 (each *s*, $2CH_3$–C(2)); 1.83 (*m*, 1H–C(8)); 2.07 (*m*, 1H–C(8), H–C(9)); 3.77 (*ddd*, *J* = 10, 8, 7, 1H–C(7)); 4.07 (*ddd*, *J* = 8, *ca.* 8, 2, 1H–C(7)); 5.48 (*d*, *J* = 6, H–C(4)); 6.06 (*d*, *J* = 6, H–C(3)). MS: 168 (3, M^+), 153 (28), 138 (4), 125 (18), 123 (88), 113 (100), 109 (16), 97 (19), 95 (81), 85 (6), 82 (28), 81 (15), 67 (41), 55 (24), 43 (59), 41 (26).

(5R,9R*)-2,2,9-Trimethyl-1,6-dioxaspiro[4.4]non-3-ene* (**1b**). IR ($CHCl_3$): 1108, 1055, 1000, 980, 865. ^{1}H-NMR (400 MHz): 0.98 (*d*, *J* = 7, CH_3–C(9)); 1.30, 1.38 (each *s*, $2CH_3$–C(2)); 1.61 (*m*, 1H–C(8)); 2.27 (*m*, 1H–C(8), H–C(9)); 3.90 (*ddd*, *J* = 8, 8, 4.5, 1H–C(7)); 3.99 (*q*, *J* = 7, 1H–C(7)); 5.62 (*d*, *J* = 6, H–C(4)); 6.03 (*d*, *J* = 6, H–C(3)). MS: 168 (3, M^+), 153 (27), 138 (4), 125 (18), 123 (85), 113 (100), 109 (16), 97 (19), 95 (80), 85 (6), 82 (28), 81 (14), 67 (41), 55 (21), 43 (52), 41 (27).

(5R,9R*)-2,2,9-Trimethyl-1,6-dioxaspiro[4.4]nonane* (**2a**). IR: 1240, 1175, 1140, 1115, 1042, 1015, 970, 925, 872. ^{1}H-NMR (400 MHz): 1.02 (*d*, *J* = 6.5, CH_3–C(9)); 1.17, 1.36 (each *s*, $2CH_3$–C(2)); 1.68–1.77 (*m*, 2H); 1.91–2.08 (*m*, 5H); 3.73 (*q*, *J* = 7.5, 1H–C(7)); 3.94 (*ddd*, *J* = 8, *ca.* 8, 2, 1H–C(7)). MS: 170 (7, M^+), 155 (48), 140 (5), 125 (26), 115 (100), 112 (31), 101 (48), 99 (15), 97 (83), 83 (20), 73 (19), 71 (18), 70 (50), 69 (51), 57 (35), 56 (48), 55 (60), 43 (66), 41 (52).

(5R,9S*)-2,2,9-Trimethyl-1,6-dioxaspiro[4.4]nonane* (**26**). IR: 1168, 1135, 1045, 1005, 980, 922, 910, 870. ^{1}H-NMR (400 MHz): 0.98 (*d*, *J* = 7, CH_3–C(9)); 1.18, 1.35 (each *s*, $2CH_3$–C(2)); 1.51 (*m*, 1H–C(8)); 1.75 (*m*, 1H); 1.90 (*m*, 1H); 1.93–2.03 (*m*, 2H); 2.19 (*ddq*, *J* = 6, 6, 4, H–C(9)); 2.26 (*m*, 1H–C(8)); 3.87 (*m*, 2H–C(7)). MS: 170 (6, M^+), 155 (50), 140 (5), 125 (27), 115 (100), 112 (33), 101 (47), 99 (18), 97 (88), 83 (22), 73 (20), 71 (19), 70 (49), 69 (54), 57 (38), 56 (52), 55 (65), 43 (75), 41 (48).

Synthesis of 1a–2b. – *2,2,9-Trimethyl-1,6-dioxaspiro[4.4]non-3-enes* (**1a/1b**). Following the procedure described for **B** [28], 4.2 g (25 mmol) of 2-methyl-3-butyn-2-yl tetrahydropyranyl ether in 50 ml of anh. Et_2O were treated at 0° with 25 ml of 1M MeLi in Et_2O. After 5 min of stirring, the solution was transferred to a stirred solution of 2.6 g (26 mmol) of α-methyl-γ-butyrolactone in 50 ml of Et_2O. After 4 h, 20 ml of 20% aq. NH_4Cl was rapidly added. The oil obtained after usual workup was dissolved in 50 ml of EtOH and hydrogenated in the presence of 0.40 g of *Lindlar* catalyst until an equimolar amount of H_2 had been absorbed. After filtration, the solution was treated with 30 ml of 10% aq. HCl for 2 h. Usual workup and subsequent bulb-to-bulb distillation gave 3.0 g of a product containing 40% of **1a/1b** (7:3) and **2a/2b** (7:3) in a ratio of 3:2 (GLC). Compounds **1a–2b** were isolated by CC (hexane/Et_2O 10:1) and prep. GLC in purities of 87–94%. The spectral data of **1a–2b** were identical with those of the corresponding natural specimens.

2,2,9-Trimethyl-1,6-dioxaspiro[4.4]nonanes (**2a/2b**). To a solution of 10.50 g (70 mmol) of rose furan (**3**; for synthesis see *e.g.* [38]) in 80 ml of CH_2Cl_2 were added, at 10–15°, 8.0 g of NaOAc and within 1 h 14.60 g (76 mmol) of 40% peracetic acid. The mixture was stirred at r.t. for 2 h, diluted with Et_2O and washed with 10% aq. Na_2CO_3 and brine. After evaporation of the solvent, the residue (**3/4** *ca.* 1:4) was chromatographed on silica gel (hexane/Et_2O 20:1) to give 6.0 g of pure *rose furan epoxide* (= 2-(2',3'-epoxy-3'-methylbutyl)-3-methylfuran; **4**). IR: 1630, 1510, 1455, 1378, 1328, 1250, 1190, 1150, 1120, 1048, 900, 888, 848, 772, 730. ^{1}H-NMR (400 MHz): 1.32, 1.38 (each *s*, each 3H); 1.99 (*s*, 3H); 2.71 (*m*, 1H); 2.95 (*m*, 2H); 6.19 (*d*, *J* = 1.5, 1H); 7.28 (*d*, *J* = 1.5, 1H). MS: 166 (13, M^+), 151 (16), 133 (2), 123 (13), 107 (8), 95 (100), 94 (16), 79 (22), 67 (16), 59 (8), 53 (8), 43 (36), 41 (45), 39 (28).

A solution of 3.0 g of **4** (17.8 mmol) in 10 ml of Et_2O was added at r.t. dropwise to a slurry of 0.35 g (9 mmol) of $LiAlH_4$ in 25 ml of Et_2O. After stirring and refluxing for 22 h, the mixture was cautiously treated with H_2O at 0° and worked up in the usual manner to give 3.5 g of **4/5** in a ratio of 2:3. CC on silica gel (hexane/Et_2O 2:1) gave 1.0 g of pure *2-(3'-hydroxy-3'-methylbutyl)-3-methylfuran* (**5**). IR: 3360, 1628, 1510, 1145, 1072, 957, 904, 888, 720. ^{1}H-NMR (60 MHz): 1.21 (*s*, 6H); 1.66 (*m*, 2H); 1.95 (*s*, 3H); 2.68 (*m*, 2H); 6.12 (*d*, *J* = 1.5, 1H); 7.20 (*d*, *J* = 1.5, 1H). MS: 168 (7, M^+), 150 (35), 135 (64), 121 (3), 117 (3), 107 (9), 95 (100), 82 (10), 79 (10), 67 (9), 59 (24), 55 (6), 43 (18), 41 (21), 39 (11).

Alcohol **5** (0.75 g, 4.5 mmol) in 5 ml of MeOH was hydrogenated over 20 mg of 10% Pd/C. After 40 min, the theoretical amount of H_2 had been absorbed. Usual workup and subsequent bulb-to-bulb distillation gave 0.35 g of product containing to 40% **2a/2b** in a ratio of 7:3. The spectral data of **2a** and **2b** (isolated *via* prep. GLC) were identical with those of the corresponding natural isomers.

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