[4] *D. G. Markees*, J. org. Chemistry *31*, 4253 (1966).
[5] *J. R. Price*, Austral. J. sci. Res. *2A*, 272 (1949).
[6] *D. G. Markees*, J. org. Chemistry *23*, 1030 (1957).
[7] *J. Meisenheimer*, Liebigs Ann. Chem. *385*, 128 (1911).
[8] *J. H. Burckhalter, F. H. Tendick, E. M. Jones, Patricia A. Jones, W. H. Holcomb & A. L. Rawlins*, J. Amer. chem. Soc. *70*, 1363 (1948).
[9] *R. E. Foster, R. D. Lipscomb, T. J. Thompson & C. S. Hamilton*, J. Amer. chem. Soc. *68*, 1327 (1946).
[10] *A. R. Surrey*, U.S. Pat. 3362954 (1968).
[11] *G. F. Duffin & J. D. Kendall*, J. chem. Soc. *1948*, 893.

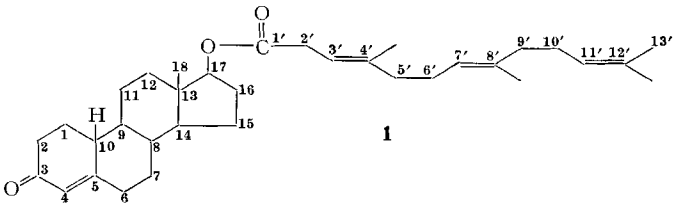
132. Terpene Compounds as Drugs, XVI. Characterization of the Anabolic 19-Nortestosterone 17β-*trans*, *trans*- and -*cis*, *trans*-Homofarnesate

by **G. Pala, A. Mantegani, E. Zugna, A. Gallazzi** and **P. C. Vanoni**
Research Laboratories, *Istituto De Angeli*, 20139 Milan, Italy

(30. 3. 72)

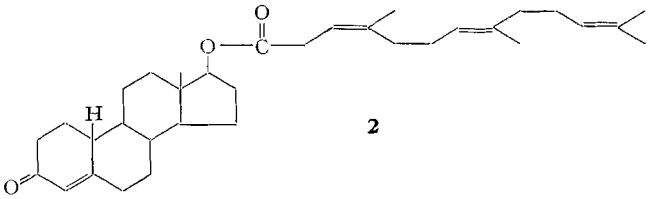
Summary. 19-Nortestosterone 17β-*trans*,*trans*- and -*cis*,*trans*-homofarnesate **1** and **2** have been prepared and characterized. Their structure and configuration were identified by mode of formation, elemental analyses, IR. and particularly by NMR. spectra.

Recently we have reported on the anabolic potency of 19-nortestosterone 17β-homofarnesate [1], as a stereoisomeric mixture consisting of 19-nortestosterone 17β-3′,4′-*trans*,7′,8′-*trans*- (**1**) and -3′,4′-*cis*,7′,8′-*trans*-homofarnesates (**2**). This paper deals with the preparation and characterization of the two stereoisomers.



1

19-Nortestosterone 17β-3′,4′-*trans*,7′,8′-*trans*-homofarnesate



2

19-Nortestosterone 17β-3′,4′-*cis*,7′,8′-*trans*-homofarnesate

19-Nortestosterone homofarnesates were obtained according to one of the methods previously described: the appropriate farnesyl bromide gave with sodium cyanide

the desired farnesyl cyanide, convertible to the corresponding homofarnesic acid which was esterified with 19-nortestosterone. Thus farnesyl bromide from *trans*-nerolidol afforded, in 32% yield, a mixture of **1** and **2** in an average ratio of 2:1.

In preliminary experiments it was found that both fractional distillation and preparative GLC. resulted in a considerable decomposition of the above mixture. The two stereoisomers were successfully separated and obtained in a highly pure state by chromatography on very fine silica gel impregnated with $AgNO_3$. **1** and **2** were then identified as 19-nortestosterone 17β-homofarnesates by elemental analyses, and their configuration determined by mode of formation, nearly identical IR. spectra, and particularly by NMR. spectra (Fig. 1 and 2, $CDCl_3$ solution).

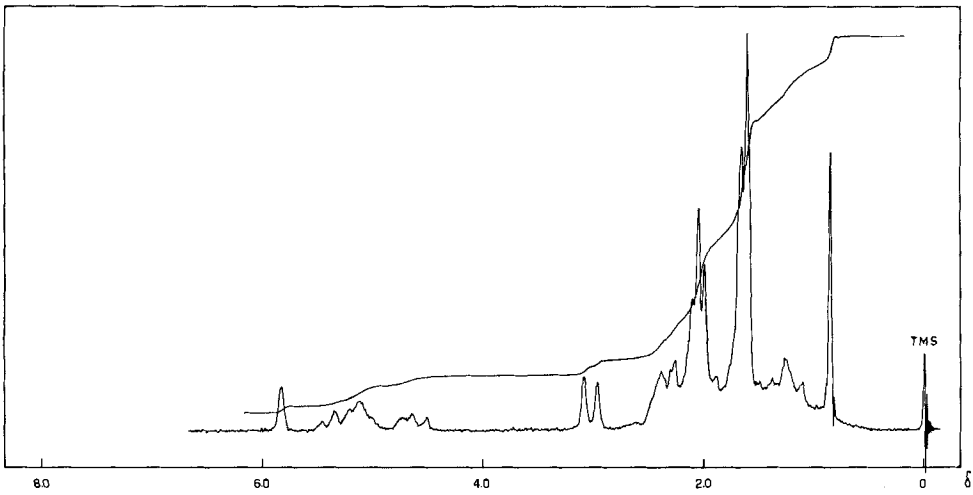


Fig. 1. *NMR. spectrum of 19-nortestosterone 17β-*trans,trans-*homofarnesate* (**1**)

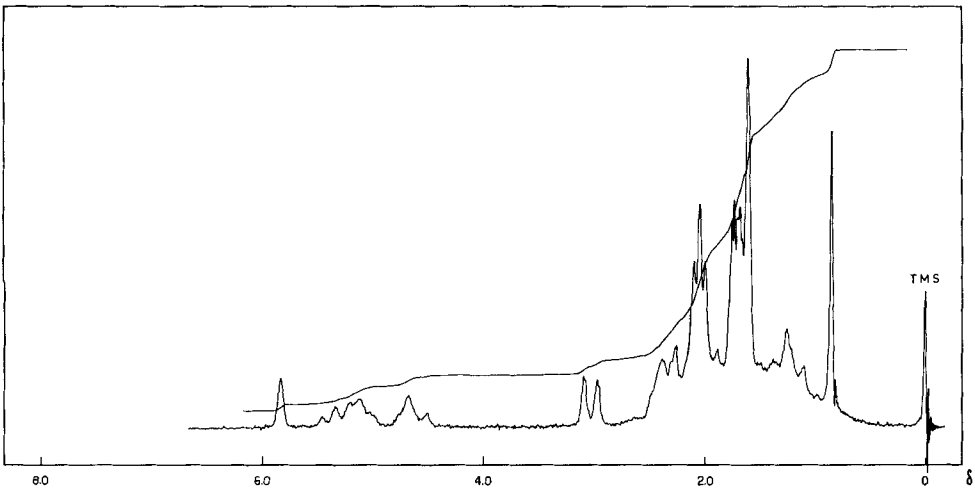


Fig. 2. *NMR. spectrum of 19-nortestosterone 17β-*cis,trans-*homofarnesate* (**2**)

In view of what has been reported on the mode of formation of the four stereoisomeric farnesols from *trans*- and *cis*-nerolidol [2], farnesyl bromide as obtained from *trans*-nerolidol would give rise, in our case, to a mixture of *trans,trans*- and *cis,trans*-homofarnesic acid in which the former is predominant. Esterification of the acid mixture with 19-nortestosterone would then give the stereochemically corresponding mixture of the esters **1** and **2**.

NMR. offered critical evidence for the configuration of **1** and **2**; the most useful information was provided by the methyl resonances. Integration and location of all the signals of the methyl protons of the two isomers were very consistent with the above stereochemical assignments. In the *trans*-configuration ($CDCl_3$ solution) the CH_3-C(4'), CH_3-C(8') and H_3C(13') protons absorb at 1.60–1.62 ppm, while in the *cis*- the CH_3-C(12') protons absorb at 1.66–1.69 ppm; these values agree well with those we recently reported for the corresponding geranyl farnesylacetates (1.60 and 1.67 ppm) [3]. As expected, in the *cis*-configuration the CH_3-C(4') protons are strongly deshielded (1.75 ppm) by the close ester group; using the technique of the solvent-induced shifts (C_6H_6) [4], these protons are caused to absorb at the same frequency (1.68 ppm) as the other *cis*-methyl protons (CH_3-C(12')) in benzene.

Another point of stereochemical interest is the long-range coupling constants observed for the CH_3-C(4') protons: in the *cis*-configuration these undergo with the adjacent C(3')-olefinic and C(2')-methylene protons *cisoid* allylic and *transoid* homoallylic couplings of 1.4 and 1.0 Hz respectively, while in the *trans*-configuration they undergo a *transoid* allylic coupling of 1.0 Hz and a very small unmeasurable *cisoid* homoallylic coupling; these findings are also compatible with the above stereochemical assignment, as it is generally accepted [4] that in unsaturated systems $J_{cisoid} > J_{transoid}$ in the order of 0.5 Hz for allylic coupling and $J_{transoid} > J_{cisoid}$ by 0.3–0.5 Hz for homoallylic coupling.

Experimental Part. – Purity of samples and composition of mixtures were determined by TLC. and NMR. The Rf values were determined on glass chromatostrips coated with silica gel GF_{254} *Merck* impregnated with $AgNO_3$; TLC. was performed with benzene/ethanol 95:5 (*v/v*); the spots were detected with a 1% solution of vanillin in concentrated H_2SO_4. UV. spectra were recorded using a *Beckman* DB-G grating spectrophotometer (EtOH). IR. spectra were recorded as liquid films using a *Perkin-Elmer* 337 grating spectrometer. NMR. spectra were run on a *Varian* A-60 A spectrometer, operating at 60.00 MHz in a radio-frequency range of 0.02–0.05 mG (sample temperature: 36°); the chemical shifts were expressed in ppm with internal tetramethylsilane as 0.00 ppm.

19-Nortestosterone 17β-trans,trans- *and* -cis,trans-*homofarnesate* (**1** *and* **2**). – a) *Preparation of the mixture.* The mixture consisting of **1** and **2** was obtained from *trans*-nerolidol in a 6.4:3.6 ratio as described in [1].

$C_{34}H_{50}O_3$ Calc. C 80.58 H 9.94% Found C 80.67 H 10.04%

Its composition was determined by hydrolysis of a sample to the corresponding isomeric homofarnesic acids, which were in turn esterified with diazomethane and submitted to GLC. examination as methyl esters.

b) *Separation of the isomers.* 20 g of the above mixture of 19-nortestosterone homofarnesates were chromatographed on 300 g of silica gel *Merck* impregnated with $AgNO_3$. After a first ineffective elution with 3 l of benzene, 1.5 l of benzene/ethanol 98:2 (*v/v*) gave 2.04 g of nearly pure **2** (fraction 1). Fraction 2 (5.4 g), obtained from a further 220 ml, had a composition rather similar to the starting material. A higher content of **1** was found in fraction 3 (6.2 g), which was obtained

on eluting with additional 260 ml of the same solvent. Further 100 ml of eluent gave 2.38 g of practically pure **1** (fraction 4).

One repetition only of this chromatography of fraction 1 gave 1.1 g of pure **2** as a colourless thick oil, $n_D^{20} = 1.5312$. TLC.: Rf = 0.55 (violet-blue). UV.: 239 nm ($\varepsilon = 17093$). IR.: 1736 (C(1')=O), 1675 (C(3)=O), 1165 (C(17)—O—C(1')), cm^{-1}. NMR. ($CDCl_3$): 0.85 (3H, $H_3C(18)$, *s*), 1.62 (6H, CH_3—C(8') and $H_3C(13')$, *d*, $J_{al} = 1.0$ Hz), 1.69 (3H, CH_3—C(12'), *d*, $J_{al} = 1.4$ Hz), 1.75 (3H, CH_3—C(4'), *d* of *t*, $J_{al} = 1.4$ Hz, $J_{ha} = 1.0$ Hz), 1.91–2.18 (8H, C(5')-, C(6')-, C(9')- and C(10')-methylene protons, *m*), 3.03 (2H, C(2')-methylene protons, *d* of *q*, $J = 7.3$ Hz, $J_{ha} = 1.0$ Hz), 4.66 (1H, C(17)-methine proton, *t* broad), 5.12 (2H, C(7')- and C(11')-olefinic protons, *t* of *qn*, $J = 6.9$ Hz, $J_{al} = 1.4$ Hz), 5.33 (1H, C(3')-olefinic proton, *t* of *q*, $J = 7.3$ Hz, $J_{al} = 1.4$ Hz), 5.83 (1H, C(4)—aromatic proton, *s*), ppm. NMR. (C_6H_6): 1.59 (6H, CH_3—C(8') and $H_3C(13')$, *s*), 1.68 (6H, CH_3—C(4') and CH_3—C(12'), *d* of *t* broad, $J_{al} = 1.4$ Hz), ppm.

One repetition only of the above chromatography on fraction 4 gave 1.5 g of pure **1** as a colourless thick oil, $n_D^{20} = 1.5297$. TLC: Rf = 0.45 (violet-blue). UV.: 239 nm ($\varepsilon = 15864$). IR.: 1736 (C(1')=O), 1675 (C(3)=O), 1160 (C(17)—O—C(1')), cm^{-1}. NMR. ($CDCl_3$): 0.85 (3H, $H_3C(18)$, *s*), 1.60 (9H, CH_3—C(4'), CH_3—C(8') and $H_3C(13')$, *d*, $J_{al} = 1.0$ Hz), 1.66 (3H, CH_3—C(12'), *d*, $J_{al} = 1.4$ Hz), 1.90–2.18 (8H, C(5')-, C(6')-, C(9')- and C(10')-methylene protons, *m*), 3.02 (2H, C(2')-methylene protons, *d*, $J = 7.3$ Hz), 4.65 (1H, C(17)-methine proton, *t* broad), 5.12 (2H, C(7')- and C(11')-olefinic protons, *t* of *qn*, $J = 6.9$ Hz, $J_{al} = 1.4$ Hz), 5.35 (1H, C(3')-olefinic proton, *t* of *q*, $J = 7.3$ Hz, $J_{al} = 1.0$ Hz), 5.83 (1H, C(4)—aromatic proton, *s*), ppm. NMR. (C_6H_6): 1.58 (9H, CH_3—C(4'), CH_3—C(8') and $H_3C(13')$, *s*), 1.68 (3H, CH_3—C(12'), *s*), ppm.

BIBLIOGRAPHY

[1] *G. Pala, S. Casadio, A. Mantegani, G. Bonardi & G. Coppi*, J. med. Chemistry, in press.
[2] *R. B. Bates, D. M. Gale & B. J. Gruner*, J. org. Chemistry *28*, 1086 (1963).
[3] *G. Pala, A. Mantegani, T. Bruzzese & G. Sekules*, Helv. *53*, 1827 (1970).
[4] *N. S. Bhacca & D. H. Williams*, "Application of NMR. Spectroscopy in Organic Chemistry"; Holden-Day, San Francisco 1964.

---

133. Thermodynamique des mélanges liquides binaires. Volume de mélange d'alcanes normaux et ramifies.

par **M. Steiger, Ch. G. Boissonnas, J. G. Fernández-García** et **H. F. Stoeckli**

Laboratoire de chimie physique de l'Université de Neuchâtel

(17 3 72)

Summary. Volumes of mixing were determined by dilatometric measurements between 15° and 50 °C for isomeric alkanes with *n*-hexadecane and *n*-dodecane. The negative excess volumes vary linearly with temperature.

Introduction. – Une étude systématique des volumes d'excès de mélanges d'alcanes normaux et ramifiés a été entreprise, pour faire suite aux mesures de *Fernandez-Garcia* [1] sur les systèmes *n*-hexadécane + isomères de l'hexane.

L'appareil, adaptable également aux mesures de chaleurs de mélange, a été décrit par Fernandez-Garcia [2]. Un dilatomètre analogue a été utisé par Duncan [3].

Résultats. – Les mesures des volumes d'excès V^E se rapportent aux solutions de l'hexadécane dans les neuf isomères de l'heptane, dans quatre isomères de l'octane et dans deux isomères du décane; aux solutions du dodécane dans quatre heptanes; aux mélanges de quelques heptanes entre eux, et au système cyclohexane + benzène.