N-analogues. Recently, various N-analogues of cardioactive cardenolides with promising pharmacological properties have been developed[41]. The compounds concerned are, e.g. 3α- and 3β-amino-3-desoxy-digitoxigenin, 3-amino-3-desoxy-derivatives of uzarigenin, oleandrigenin, gitoxigenin and digoxigenin prepared by Meyer et al.[63,64]. The same new class of compounds has been treated in several publications and has been the object of patent applications[65,66]; its therapeutic applicability is still being evaluated.

In conclusion, of the dogmas concerning structure-activity relationships as postulated by Tamm[32] and others[34,67] only those touching the 17β-configuration of the side chain and a cis configuration of the C/D-rings (i.e. 14β-H or some other 14β-substituent for possible exceptions[35,65]), are still valid. All other structural features, such as are found e.g. in digitoxigenin, do not necessarily involve a complete loss of effectiveness when modified. But none of the various structural modifications have, up to now, resulted in a compound with either pharmacological properties superior to classical cardiac glycosides or with a better therapeutic index. The hope, however, that further partially synthetic modifications will realize this goal is certainly justified.

63 L. Sawlewicz, E. Weiss, H. H. A. Linde and K. Meyer, Helv. chim. Acta *55*, 2452 (1972).
64 E. Hauser, U. Boffo, L. Meister, L. Sawlewicz, H. H. A. Linde and K. Meyer, Helv. chim. Acta *56*, 2782 (1973).
65 U. Stache, W. Haede, W. Fritsch, K. Radscheit and E. Lindner, DOS 2013032 (1971), CA 76, 14816 b (1972).
66 K. Meyer, DOS 2137047 (1972), CA 76, 141218, CA 84, 59879.
67 R. Mutschler, in: Arzneimittelwirkungen, 1. Aufl., p. 236. Wissenschaftl. Verlagsgesellschaft, Stuttgart 1970.

SPECIALIA

The editors do not hold themselves responsible for the opinions expressed in the authors' brief reports. – Les auteurs sont seuls responsables des opinions exprimées dans ces brèves communications. – Für die Kurzmitteilungen ist ausschliesslich der Autor verantwortlich. – Per le brevi comunicazioni è responsabile solo l'autore. – Ответственность за короткие сообщения несёт исключительно автор. – Solo los autores son responsables de las opiniones expresadas en estas comunicationes breves.

On the cyclization of farnesic acid[1]

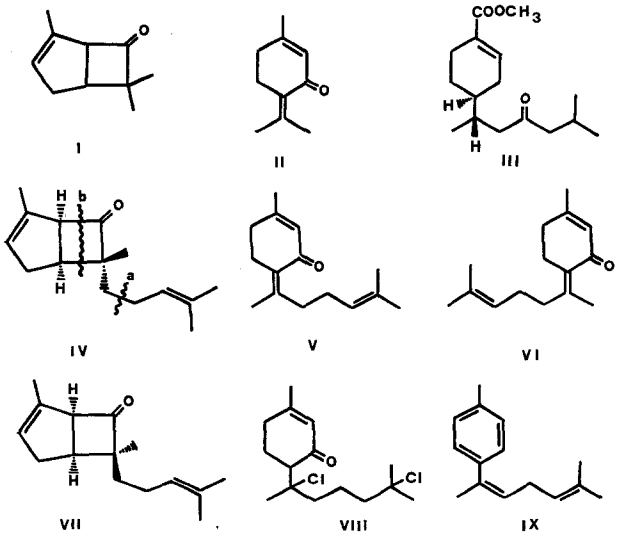
A. Corbella, P. Gariboldi, Myrna Gil-Quintero, G. Jommi and J. St. Pyrek[2]

Laboratorio di Chimica Organica, Facoltà di Scienze, Università degli Studi, via Saldini 50, I-20133 Milano (Italy),

9 September 1976

Summary. Acetic anhydride treatment of farnesic acids leads to the expected cyclohexenones (**V** and **VI**) and to the alternative formation of the [3. 2. 0]-bicycloheptenones (**IV** or **VII**) depending on the geometry of the central double bond of the acid.

The reaction of geranic acid with acetic anhydride and sodium acetate has been reported[3] to give mainly 2 products, filifolone (**I**) and piperitenone (**II**). In the search of compounds with potential hormonal activity on insects, we have done an analogous reaction with the farnesic acids on the basis of the following arguments. The esters of farnesic acids[4] display JH activity on a number of insects, but it is not known whether the compound is active as such or whether a metabolite is the true hormone.



Furthermore, some of the possible cyclization products of the farnesic acids resemble the molecule of juvabione (**III**), so that it would be of some interest to test their activity. Again, filifolone itself has been shown to display juvenoid activity on some insects[5].

Treatment of a mixture of 2-trans,6-trans- and 2-cis,6-trans-farnesic acids with acetic anhydride and sodium acetate in the conditions described by Beereboom[3] gave 3 main products which have been separated[6] by repeated silica-gel columns and identified as **IV**, **V** and **VI**.

Assignment of the structure **IV** to the compound of higher volatility is based mainly on its physicochemical data and on considerations of the reaction mechanism. The IR-spectrum has an absorption band at 1770 cm^{-1} due

1 This work has received financial support from Consiglio Nazionale delle Ricerche.

2 Present address: Inst. Org. Chem. PAN, Kasprzaka 44, Warszawa, Poland.
3 J. J. Beereboom, J. org. Chem. *30*, 4230 (1965).
4 See for references: K. Šlama, M. Romaňuk and F. Šorm, Insect Hormones and Bioanalogues. Springer-Verlag, Wien, New York 1974.
5 Unpublished results.
6 Conversion of farnesic acid is about 60%, the remaining being recovered unchanged. The yields of **IV**, **V** and **VI**, as a mean of 3 runs, are 40, 32 and 28% respectively. Column chromatography on silica-gel (absorbent:substance 30:1) eluting with hexane:AcOEt 95:5, easily separates **IV** from **V** and **VI**; these can be obtained in pure form only by a second chromatography (absorbent : substance 120 : 1) eluting with hexane : AcOEt 9 : 1.

to a cyclobutanone; the MS has 2 main peaks at 69 and 138 m/e arising from fragmentations a and b respectively; fragment a shows that the first isoprene unity is not implied in the cyclization, while fragment b is indicative of the presence of a [3.2.0]-bicycloheptenone system, from which a methylcyclopentadiene molecule is easily lost. In the NMR-spectrum it is possible to show the isopropylidene moiety (2 methyl signals at 1.60 and 1.65 δ with a long range coupling to a proton on double bond at 5.0 δ), a vinyl methyl at 1.72 δ coupled with a second proton on double bond at 5.3 δ; again, there is a multiplet at 3.85 δ for the proton on the ring junction adjacent to the carbonyl group and a tertiary methyl at 1.05 δ.

The relative stereochemistry shown in structure **IV** is based mainly on the study of molecular models[7,8]: the cyclization of the ketene, initially formed from farnesic acid, on the central double bond of the molecule leaves the tertiary methyl group on the opposite side of the hydrogens of the ring junction if the double bond has an E configuration, whereas the same methyl is cis to the hydrogens of the junction if the double bond has a Z configuration.

To confirm this point, we have repeated the reaction starting from a mixture of 2-cis,6-cis- and 2-trans,6-cis-farnesic acids. GLC analysis[9] of the crude mixture shows again 3 main products; the retention times of 2 of them (as well as their MS) coincide with those of **V** and **VI**, whereas the compound of higher volatility has a retention time slightly different from that of **IV**.

Structure **VII** has been attributed to this new compound: its IR and NMR are very similar to those of compound **IV** as well as most of the NMR-spectrum. The only meaningful difference is the chemical shift of the tertiary methyl, which, in this case, is at 1.20 δ. These data are in agreement with a different shielding effect of the π-electrons of the double bond of the ring on the tertiary methyl: when this is trans to the junction as in **IV**, it falls very near to the lobes of the double bond, when it is cis it lies well outside the influence of these electrons. The structure of **V** and **VI** derives immediately from their physicochemical data. While this work was in progress, a paper appeared in a Japanese journal[10] concerning the cyclization of farnesic acid chlorides with Lewis acids. The authors obtain mainly mono- and dichlorinated compounds such as **VIII**; on dehydrochlorination with LiCl they obtain a mixture of compounds which we found identical with **V** and **VI**.

Another compound having a very low retention time in GLC is always present in the reaction mixture, although in very small amounts. Structure **IX** has been attributed to it on the basis of the following data: UV-spectrum with a maximum at 242 nm (ε=11,000), IR with aromatic bands at 3030 cm^{-1}, MS with the molecular ion at 200 m/e and main fragments at 157, 132, 91, 69 m/e. In the NMR-spectrum, a 4-protons double doublet due to aromatic protons at 7.0 and a methyl on benzene ring at 2.28 δ are easily recognizable; furthermore there are 2 vinyl protons at 4.85 and 5.05 δ and 3 vinyl methyls at 1.50 (3H) and 1.62 δ (6H). The biological activity of the compounds so far obtained is now under investigation.

7 We have confirmed the suggestion made by Erman and coll.[8] that also in the conditions described for the synthesis of filifolone, an unsaturated ketene first cyclize to a [3.1.1]-bicycloheptenone system and then rearranges to the [3.2.0]-bicycloheptenone system. This and other related results will be discussed in a following paper.

8 W. F. Erman, R. S. Treptow, P. Bazukis and E. Wenkert, J. Am. Chem. Soc. *93*, 657 (1971).

9 A 2-m-column, filled with 10% Carbowax 20M on Chromosorb was used; linearly programmed temperature from 130 to 180 °C, gradient 10 °C/min.

10 K. Tobayashi, S. Kumazawa, T. Kato and Y. Kitahara, Chem. Lett. *301* (1975), C. A. *83*, 28380.

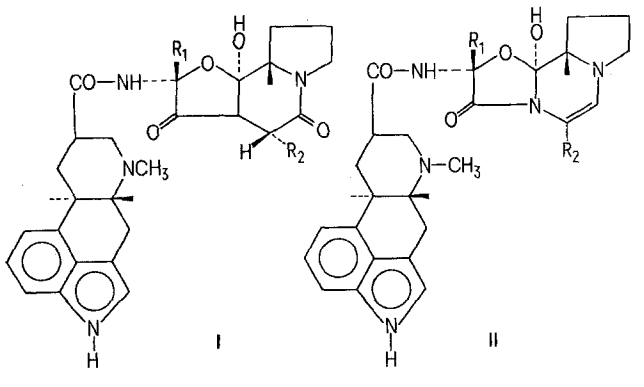
Ergot alkaloids modified in the cyclitol moiety

L. Bernardi and G. Bosisio

Farmitalia, Ricerca Chimica, Laboratori di Milano, Via dei Gracchi, 35, I-20146 Milano (Italy), 8 June 1976

Summary. Birch reduction of 9,10-dihydroergot alkaloids (**I**) yields a compound to which structure **II** is assigned.

In recent years the preparation, via total synthesis, of ergot alkaloids modified in the cyclitol moiety, has been intensively investigated[1]; however no attempt has been so far made to modify directly the peptide residue of the natural alkaloids. In the present note we report the selective reduction of the 6′ carbonyl group of 9,10-dihydroergot alkaloids (**I**) by litium in liq. ammonia to give the 6′-desoxy-5′, 6′-didehydroderivatives (**II**).



Portionwise treatment of dihydroergotamine (**I**; R_1 = CH_3; R_2 = $CH_2C_6H_5$) (10.3 mmoles) in liq. NH_3 (900 ml) with litium (30 mmoles) at −35 °C yielded a new compound, less polar than the starting material, that still gave a blue color with the Van Urk reagent, thus indicating that the indole nucleus, contrary to the expectations, had been unaffected[2]. Minor by-products were also present as shown by TLC, but since with this reagent they gave a yellowish-green color typical for the 2,3-dihydroergolines[5], they were not further investigated.

The new compound, purified by chromatography on silicagel column (60% yield; m.p. 207–208 °C; $[\alpha]_D^{20}$ −50°, Py) had a molecular formula $C_{33}H_{37}N_5O_4$ corresponding to a loss of the 1 oxygen atom from dihydroergotamine, the mass spectrum[6] showed a peak at m/e 269 (dihydrolysergamide) and 298 (reduced cyclol moiety), and on treatment with a dilute solution of oxalic acid at room tem-