Zusammenfassung. In diesem Übersichtsreferat werden die Stoffwechselstudien mit dem Schlafmittel Doriden® (α-Phenyl-α-äthyl-glutarimid) geschildert, wobei alle bisher erzielten, teilweise noch nicht veröffentlichten Resultate zusammengefasst sind. Die Untersuchungen wurden an Ratten und Hunden mit Hilfe von ^{14}C-markierter Substanz durchgeführt, speziell im Hinblick auf die Abklärung der Resorption, Verteilung, Ausscheidung und Struktur der Metaboliten des Wirkstoffes. Es wurde gefunden, dass Doriden nach der Resorption in kurzer Zeit praktisch quantitativ in Form von Metaboliten im Harn ausgeschieden wird. Diese bestehen zu mehr als 90% aus Glucuroniden, welche untoxisch sind und keine sedative Wirkung mehr besitzen. Aus der Strukturaufklärung der isolierten Stoffwechselprodukte ging hervor, dass Doriden nach zwei verschiedenen biochemischen Mechanismen metabolisiert wird, und es konnte gezeigt werden, dass dies auf den verschiedenen Stoffwechsel der beiden Antipoden von α-Phenyl-α-äthyl-glutarimid zurückzuführen ist. Versuche mit Gallenfistelratten liessen erkennen, dass 70% der Glucuronide über die Galle und 30% direkt renal ausgeschieden werden. Bei einer solchen Versuchsanordnung konnte eine biologische Halbwertszeit von Doriden von 6,5 h bestimmt werden. Verteilungsstudien mit ^{14}C-markiertem Doriden und mit markierten Glucuroniden nach oraler und parenteraler Gabe liessen erkennen, dass sich Doriden ähnlich wie die ultrakurzwirksamen Barbiturate verhält, indem es eine ausgesprochene Affinität zu lipoidem Gewebe aufweist. Die Glucuronide dagegen sind aus dem Magen-Darm-Trakt bedeutend schlechter resorbierbar, zeigen keine Affinität zu lipoiden Organen und werden – einmal im Blut angelangt – durch die Niere rasch und vollständig eliminiert.

Brèves communications – Kurze Mitteilungen – Brevi comunicazioni – Brief Reports

On the Structure of Ryanodol

Ryanodine, $C_{25}H_{35}O_9N$, a constituent of *Ryania speciosa* Vahl., represents a challenging structural problem due to its heavy oxygen substitution and the consequent complexity of its reactions. As reported earlier[1], it is an ester of pyrrol-α-carboxylic acid with ryanodol, $C_{20}H_{32}O_8$.

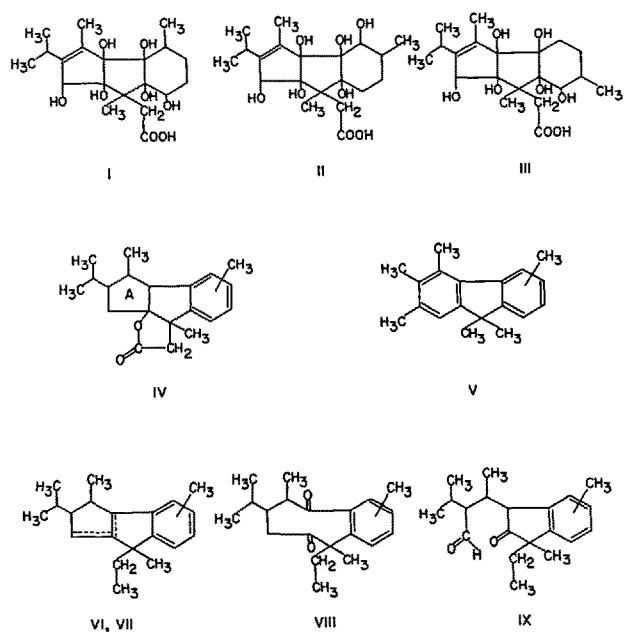
A mild acidic treatment of ryanodol converts it to anhydroryanodol, $C_{20}H_{30}O_7$, which consumes 1 Mol of periodic acid to give oxoanhydroryanodol, $C_{20}H_{28}O_7$[2,3]. In a recent communication[3], we have reported the alkaline cleavage of oxoanhydroryanodol into several fragments of known structure which accounted for all the carbon atoms of this compound.

We have now in principle solved the structure of anhydroryanodol and the mechanism by which it yields the above mentioned fragments. *Anhydroryanodol must be represented as a lactone of one of the three hydroxyacids I–III.*

The most important clue for the skeletal type of anhydroryanodol was provided by the treatment of ryanodol with hydriodic acid and red phosphorus. This reaction gave a mixture of products from which the γ-lactone IV, $C_{20}H_{26}O_2$, m.p. 135–138°, was isolated in a good yield[4].

The clue to the structure of IV came in turn from the selenium dehydrogenation of an amorphous fraction obtained in the same reaction. This dehydrogenation gave an aromatic compound, $C_{19}H_{22}$, m.p. 122–124°, which is clearly a fluorene (UV) and which can be formulated as V on the basis of its NMR spectrum, and of its origin (NMR maxima: singlet (6H) at 8.63 ppm, 2 benzylic methyls; 4 singlets (3H each) at 7.40, 7.60, 7.68, and 7.77 ppm, aromatic methyls; multiplet (4H) at 2.4–3.0 ppm, aromatic hydrogens).

The structural studies performed on IV are too lengthy to describe in a short communication. Suffice it to say



[1] R. B. Kelly, D. J. Whittingham, and K. Wiesner, Can. J. Chem. *29*, 905 (1951).
[2] R. B. Kelly, D. J. Whittingham, and K. Wiesner, Chem. and Ind. *1952*, 857.
[3] D. R. Babin, J. A. Findlay, T. P. Forrest, F. Fried, M. Götz, Z. Valenta, and K. Wiesner, Tetrahedron Letters No. *15*, 31 (1960).
[4] All new compounds reported in this communication gave satisfactory analyses.

that they included the conversion of IV into the two unsaturated isomers VI and VII and the two *seco*-derivatives VIII and IX. A preparative Kuhn-Roth oxidation of IV gave a mixture of isobutyric and acetic acid and the NMR spectrum of IV is in good agreement with the structure assigned (see Table I). The placement of the methyl and isopropyl groups in the ring A of IV follows from the properties of compound IX and from the connection of IV with anhydroryanodol (*vide infra*).

Table I. The NMR spectrum of the γ-lactone IV

Position in ppm (relative to Me_4Si)	Number of Hydrogens	Splitting	Assignment
3.02	3	Singlet	Aromatic H
6.88	1	Doublet	Benzylic H
7.50	2	Singlet	CH_2–COO–
7.70	3	Singlet	Aromatic CH_3
7.90–8.60	5	Multiplet	Aliphatic CH_2 + CH
8.60	3	Singlet	Benzylic CH_3
8.67, 9.01, 9.23	9	Doublets	3 C–CH_3

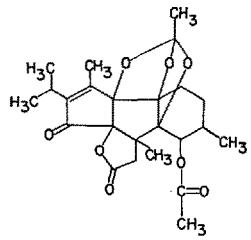
A further clarification of the structural problem resulted from studies on anhydroryanodol itself. A particularly simple derivative of this compound is the *ortho*-acetate diacetate, $C_{26}H_{34}O_9$, m.p. 227°. It may be hydrolysed with alkali to an *ortho*-acetate monoacetate, $C_{24}H_{32}O_8$, m.p. 272°, which oxidizes with chromium trioxide in pyridine to the corresponding ketone, $C_{24}H_{30}O_8$, m.p. 262°. The ultraviolet (max. 237.5 mμ, log ε 4.03) and infrared (max. in KBr at 1768, 1738, 1710, and 1619 cm^{-1}) spectra of this last compound clearly show the presence of a γ-lactone and a completely substituted *cyclo*pentenone ring, while its NMR spectrum (see Table II) defines the substitution of these two rings.

Table II. The NMR spectrum of the orthoacetate monoacetate ketone

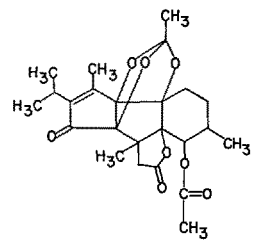
Position in ppm	Number	Splitting	Assignment
4.28	1	Doublet	CH–O–C(=O)–CH_3
7.46	2	Singlet	CH_2–COO
7.83	3	Singlet	Acetyl
7.94	3	Singlet	CH_3–C=C–C=O
8.26	9	Singlet	CH_3–C(–O–)(–O–)–O–
8.2–8.5		Multiplet	CH_2 + CH
8.72	6	Doublet	Isopropyl
8.9	3	Singlet	CH_3–C(–C)–C
9.05	3	Doublet	CH_3–CH

On the basis of formula III, this ketone may be represented as X or XI (corresponding formulations based on I and II are omitted to economize with space).

The most important test of these structures is the fact that they allow a very simple interpretation of the alkaline cleavage of oxoanhydroryanodol[3] (formulated as a lactone

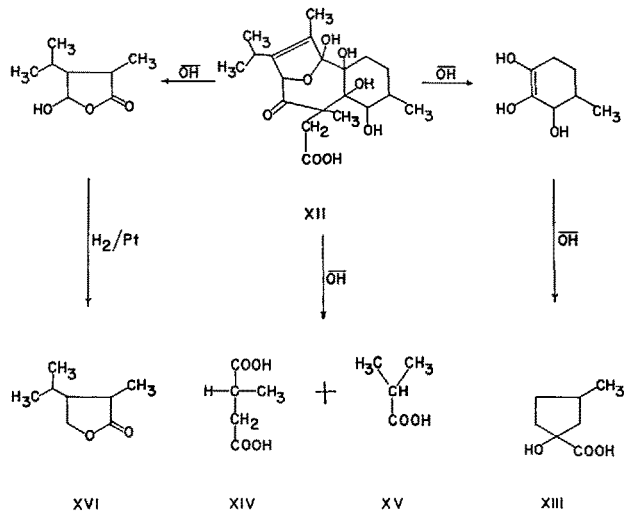


X



XI

of XII on the basis of III) into the identified fragments XIII, XIV, XV, and XVI. This interpretation follows from the corresponding formula scheme which is self-explanatory.



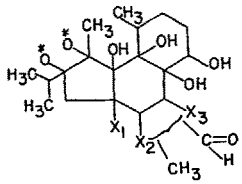
XVI XIV XV XIII

The structural clarification of anhydroryanodol makes it possible to formulate the principle features of ryanodol itself when the following additional facts are considered: (1) Extensive partly published evidence[3] makes it clear that ring B of ryanodol is six-membered and substituted by a hemiacetal carbon; (2) permanganate-periodate oxidation of ryanodol yields acetic, isobutyric and α-methylglutaric acid; (3) ryanodol contains six hydroxyl groups (D exchange); (4) NMR spectra of various ryanodol derivatives show the presence of only one secondary O-function in addition to the hemiacetal group. All the remaining O-functions must be tertiary.

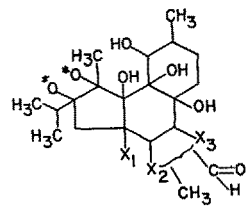
Ryanodol can thus be represented by one of the general formulae XVII, XVIII, or XIX. In these formulae, one of the groups X_1, X_2, and X_3 is a hydrogen atom, while the remaining two are oxygen functions. In addition, the aldehyde group is present as a hemiacetal and the second oxygen ring is either an epoxide (in place of the two O*-atoms) or a larger oxide in which one of the O*-atoms is attached at X_1, X_2, or X_3.

For clarity, formulae XX and XXI are given as possible complete expressions for ryanodol. *Our present evidence does not, however, exclude alternative structures contained in the general formulation XVII → XIX.* The formation of anhydroryanodol from ryanodol thus involves three main processes, an ether-opening, an allylic rearrangement in ring A and a Wagner rearrangement in ring B.

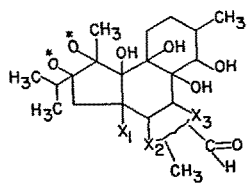
It might be argued that, biogenetically speaking, the skeleton of structure XVIII is simply a combination of the nepetalic acid skeleton with a normal monoterpene and is thus formed from two monoterpenoid units. Since in structures XVII and XIX the second unit is not mono-



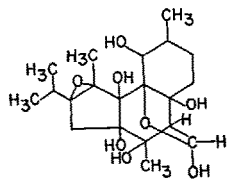
XVII



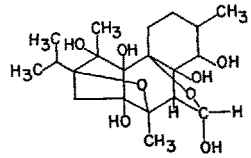
XVIII



XIX



XX



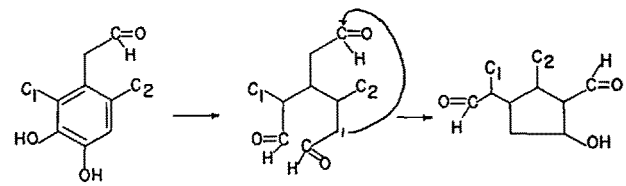
XXI

terpenoid, this argument would make XVIII *a priori* more likely. In our opinion this reasoning is not permissible since the terpenoid origin of the nepetalic acid skeleton is also uncertain.

Recently, THOMAS[5] postulated that the correspondence in structures between the nontryptamine portion of indole alkaloids and the various substances possessing the nepetalic acid skeleton may be explained by discarding the well-known theories of indole alkaloid biogenesis and assuming that the nontryptamine portion of the indole alkaloids is formed by cleavage of a monoterpene with the nepetalic acid skeleton.

We should like to point out that the published data can be explained by an alternative theory which is *a priori* completely equivalent to the THOMAS hypothesis: Compounds with the nepetalic acid skeleton can be biosynthesized by a route involving a Woodward fission of an alkylated phenylacetaldehyde and the resemblance of the product to a terpenoid can be purely coincidental. Such a possible biosynthesis is portrayed in the structures XXII, XXIII, and XXIV.

It is clear that the decision between these two possibilities will have to come from biochemical experiments. In the meantime, however, it does not seem permissible to use the isoprene rule for structural arguments in ryanodine chemistry[6].



XXII XXIII XXIV

Zusammenfassung. Anhydroryanodol besitzt eine den Strukturen I, II oder III entsprechende Laktonformel. Die Struktur des Ryanodols ist in der allgemeinen Formulierung XVII–XIX enthalten. Das Problem der Ryanodolbiogenese wird kurz diskutiert.

Z. VALENTA and K. WIESNER[7], in collaboration with D. R. BABIN, T. BÖGRI, T. P. FORREST, F. FRIED, and H. REINSHAGEN

Organic Chemistry Laboratory, University of New Brunswick (Canada), December 20, 1961.

[5] R. THOMAS, Tetrahedron Letters No. *16*, 544 (1961).

[6] *Acknowledgments.* This work was supported at various stages by the National Research Council, Ottawa, the Research Corporation, New York, the Ciba Company, Summit (New Jersey), the Schering Corporation Ltd., Montreal, and the Hoffmann-La Roche Inc., Nutley (New Jersey). The large amounts of powdered *Ryania speciosa* which were required were donated by S. B. Penick and Company, New York. We wish to thank Professor K. BIEMANN, Massachusetts Institute of Technology, Cambridge, for the mass spectroscopic molecular weight determination of the lactone IV.

[7] The contribution of all our collaborators will be discussed in several papers to be published in the near future.

Mass Spectrometry in Structural and Stereochemical Problems[1] Spegazzinine and Spegazzinidine[2]

A few years ago, we reported[3] the isolation of (−)-quebrachamine[4] and of a new phenolic dihydroindole alkaloid, spegazzinine, from *Aspidosperma chakensis* Spegazzini. With the amount then at our disposal, we were only able to characterize the functional groups and to demonstrate the partial structure I; no firm decision could be reached between the empirical formulae $C_{21}H_{28}N_2O_3$ and $C_{22}H_{30}N_2O_3$, although the former was preferred because of a presumed relationship to aspidospermine (II)[5]. When additional plant material became available, we resumed this investigation, but found that the new extract contained only small quantities of spegazzinine, the principal alkaloid being a new phenolic one, which we have named spegazzinidine. Using mass spectrometry and nuclear magnetic

[1] This paper represents part III. For preceding paper see B. GILBERT, J. FERREIRA, R. J. OWELLEN, C. E. SWANHOLM, H. BUDZIKIEWICZ, L. J. DURHAM, and C. DJERASSI, Tetrahedron Letters, *1962*, 59.

[2] This paper represents Part VI in the La Plata series *Estudios sobre Plantas*; for paper V see T. NAKANO, C. DJERASSI, R. A. CORRAL, and O. O. ORAZI, J. org. Chem. *26*, 1184 (1961).

[3] O. O. ORAZI, R. A. CORRAL, J. S. E. HOLKER, and C. DJERASSI, J. org. Chem. *21*, 979 (1956); Anales Asoc. Quim. Argentina *44*, 177 (1956).

[4] K. BIEMANN and G. SPITELLER, Tetrahedron Letters *1961*, 299.

[5] J. F. D. MILLS and S. C. NYBURG, J. chem. Soc. *1960*, 1458. See also G. F. SMITH and J. T. WROBEL, J. chem. Soc. *1960*, 1463, and H. CONROY, P. R. BROOK, and Y. AMIEL, Tetrahedron Letters No. 11, 4 (1959).