but also represents a new helpful tool in the structural elucidation of terpenic compounds. This new tool limits the number of carbon skeletons which can be proposed on the basis of the original isoprene rule[1] ("*empirical isoprene rule*") alone. It is obvious that any formula deduced in accordance with the "biogenetic" as well as with the "empirical" isoprene rule requires experimental proof.

The "empirical isoprene rule" was deduced formally from the structure of the natural terpenic compounds. From the "biogenetic isoprene rule", however, it would follow that the carbon skeleton of the biological end product is not necessarily identical to the carbon skeleton of the precursor. In other words the validity of the "empirical isoprene rule" depends on the mechanisms of formation of the natural compounds, and the failure of a terpene to obey this rule does not necessarily disprove its origin from isoprene units.

Nomenclature

The terms terpene, diterpene, triterpene are retained here in preference to the terms terpenoid, diterpenoid, triterpenoid, which are occasionally used in the modern literature. These terms have unnecessarily been introduced in analogy to the expression "steroid", which denotes a group of compounds having an irregularly varying number of carbon atoms. In the terpenic field the expression terpenoid should be reserved by analogy for compounds in which the number of carbon atoms varies irregularly[2], in contrast to the terpenes proper, where the number of carbon atoms is always a multiple of five.

The terms monoterpene, sesquiterpene, diterpene, triterpene are unambiguous and need not be replaced by nebulous synonyms ending in "oid". The term terpene, on the other hand, originally designated the monoterpenes alone. In order to avoid confusion the term terpene should be used only to designate the whole class of the terpenic compounds, and for the C_{10} group the term monoterpene should be used exclusively.

Zusammenfassung

Es wird eine Übersicht über die Kohlenstoffgerüste der Sesquiterpene, Diterpene und Triterpene gegeben. Die Isoprenregel zeigt in jeder dieser Gruppen besondere Eigenheiten. Auch die C_{30}-Steroide und ein Steroid mit 31 Kohlenstoffatomen, die mit den Triterpenen verwandt sind, werden besprochen. Die Zusammenhänge zwischen Diterpenen und Triterpenen in bezug auf ihre Konstitution und Konfiguration werden diskutiert, wobei auf die weitgehende Übereinstimmung ihrer Konfiguration mit der Konfiguration der Steroide hingewiesen wird. Die kürzlich durch die Experimentalarbeiten von Bloch gewonnenen Kenntnisse über die biologische Entstehung des Cholesterins aus Essigsäure, unter sehr wahrscheinlicher Zwischenbildung des Triterpens Squalen, geben Anlass zur Erörterung hypothetischer Wege für die Biogenese der pentazyklischen Triterpene aus Squalen, der zyklischen Sesquiterpene aus Farnesol, der zyklischen Diterpene aus Geranyl-geraniol und schliesslich auch der zyklischen Monoterpene aus Geraniol, unter Beachtung der elektronischen Zyklisierungsmechanismen der organischen Chemie. Schliesslich wird die «biogenetische» Isoprenregel definiert und ihre Bedeutung diskutiert.

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[1] *Cf.* page 357.

[2] *E.g. santene (C_9), irone (C_{14}), lupulone (C_{21}).*

Brèves communications - Kurze Mitteilungen
Brevi comunicazioni - Brief Reports

The Configuration of Digoxigenin

Although crystalline Digoxin (the tridigitoxoside of digoxigenin) was isolated in 1930[1] and has been in clinical use in the United Kingdom since 1933[2] the accepted proof of its structure is vitiated by a discrepancy between the optical rotation of the derived methyl 3:12-dihydroxyetianate, $[\alpha]_D + 39^\circ$ (methanol)[3] and of authentic methyl $3\alpha:12\beta$-dihydroxyetianate, $[\alpha]_D + 52^\circ$ (methanol)[1], with which it gave no melting point depression[2]. This matter was discussed with Professor Reichstein and Dr. D. A. H. Taylor in 1952 and in the knowledge that the former was planning to prepare the four isomeric 3:12-dihydroxyetianates and the latter was repeating the degradation of digoxigenin, we studied partial acetylation of digoxigenin and the anhydrodigoxigenins.

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[1] S. Smith, J. Chem. Soc. *1930*, 508.

[2] Brit. Med. J. *295*, 364 (1933).

[3] M. Steiger and T. Reichstein, Helv. chim. Acta *21*, 828 (1938).

[1] V. Wenner and T. Reichstein, Helv. chim. Acta *27*, 965 (1944).

[2] M. Steiger and T. Reichstein, Helv. chim. Acta *21*, 828 (1938). – H. L. Mason and W. M. Hoehn, J. Amer. Chem. Soc. *60*, 2824 (1938); *61*, 1614 (1939).

Digoxigenin on attempted partial acetylation gave mixtures of the diacetate and digoxigenin with no trace of monoacetates. "β"-Anhydro (Δ 14) digoxigenin however gave the 12-monoacetate, m.p. 199° $[\alpha]_D + 26°$ (chloroform), whilst "α"-anhydro(Δ8–14)digoxigenin gave a complex mixture from which a little of the 3-monoacetate, m.p. 218° $[\alpha]_D + 31°$ (chloroform) was isolated. The derived molecular increments of rotation on acetylation of the 3-hydroxy group were $+28$ and -15 respectively, and clearly support a 3β-configuration (standard value $+17 \pm 17$) rather than a 3α-configuration (standard value $+83 \pm 30$)[1]. In addition, "α"-anhydrodigoxigenin-3-monoacetate shows a complex band in the infra-red at 8 μ, characteristic of a 3β-acetoxycholane derivative[2]. The formulation of digoxigenin as 3β:12β:14-trihydroxycard–20:22-enolide with a 3β-"polar" hydroxy group and a 12β-"equatorial" hydroxy group which is hindered by the 14β-hydroxy group satisfactorily explains the partial acetylation experiments.

Digoxigenin, therefore, like all known cardiac aglycones of proved chemical structure, has a 3β-hydroxy group.

H. M. E. Cardwell and S. Smith

The Dyson Perrins Laboratory, Oxford University, and Dartford, Kent, 10 June, 1953.

Zusammenfassung

Partielle Azetylierung von Digoxigenin und den Anhydrodigoxigeninen hat ergeben, dass dem Digoxigenin die Struktur 3-β; 12-β,14-Trihydroxy-card 20 (22)-enolid zukommt.

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[1] D. H. R. Barton, J. Chem. Soc. *1946*, 1116.

[2] R. N. Jones, P. Humphries, F. Herling, and K. Dobriner, J. Amer. Chem. Soc. *73*, 3215 (1951).

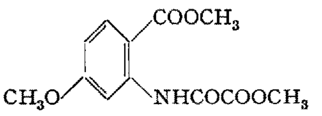
On the Constitution of Reserpine from *Rauwolfia serpentina* Benth[1]

In an earlier communication[2] we have demonstrated that reserpine[3], a hypnotic and hypotensive alkaloid, isolated from *Rauwolfia serpentina* Benth[4], can be hydrolyzed to reserpic acid, trimethoxybenzoic acid and methanol.

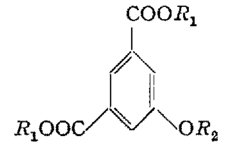
$$C_{33}H_{40}O_9N_2 + 2H_2O \longrightarrow C_{22}H_{28}O_5N_2 + C_{10}H_{12}O_5 + CH_3OH$$

The original alkaloid could be reconstituted by the interaction of methylreserpate with trimethoxybenzoylchloride in pyridine solution and it was thus demonstrated that reserpic acid, the key-compound in the chemistry of reserpine, does not suffer from any secondary changes during hydrolysis.

Oxidation of reserpic acid with potassium permanganate under conditions used in the indole alkaloid field by earlier investigators[5] has yielded 4-methoxy-oxalyl-anthranilic acid (isolated as its ester I). By potash fusion we have obtained an acidic fraction, which, after methylation, yielded the symmetric 5-methoxyisophthalic acid dimethyl ester (II). Both compounds were identical with synthetic products[1]; their I.R. spectra were identical and no depression of mixed melting point was found.



I



II: $R_1 = R_2 = CH_3$
III: $R_1 = H$; $R_2 = C_2H_5$

As it was possible that the methoxyl group of the ester (II), was an artefact, the acidic fraction of the potash fusion was ethylated with diazoethane. The crude ester was a liquid at room temperature, crystallizing at $-20°$. It was therefore hydrolyzed and 5-ethoxyisophthalic acid (III), identical with a synthetic product, was obtained. It was thus demonstrated that 5-hydroxyisophthalic acid was present originally. This does not necessarily imply that the phenolic hydroxyl of the isophthalic acid represents the alcoholic group of reserpic acid, but for biogenetical reasons it is quite likely.

When reserpic acid hydrochloride was treated with acetic anhydride in pyridine, a lactone, $C_{22}H_{26}O_4N_2$, m.p. 335° could be obtained in 60% yield, which was best isolated as a hydrochloride. The same compound was obtained with acylchlorides generally, but the isolation of the pure compound, in this case, was more difficult. The presence of a γ-lactone is supported by I.R. evidence, which would fit into our conceptions concerning the positions of the carboxyl and the alcoholic hydroxyl groups. Spectral evidence indicates that reserpic acid contains a monomethoxylated tetrahydro-β-carboline system. This assumption is further substantiated by a positive Adamkiewicz color test, which is not, as stated in the literature[2], typical for a carboxylic acid of the harman series, but for tetrahydroharman derivatives themselves. This color reaction has been studied with more than 20 indole alkaloids and found to be correct in all cases[3].

Furthermore, the isolation of the isophthalic acid derivative makes it likely that reserpic acid is a derivative of yohimbane[4]. For the time being, we postulate this working hypothesis and if this is accepted, it is evident that acid (I) is derived from rings *A* and *B* and acid (II) from ring *E* of the yohimbane skeleton. Although full experimental information concerning rings *C* and *D* is not yet available, we propose the following structure for reserpic acid (IV)[5].

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[1] Communication 7 on *Rauwolfia* Alkaloids.

[2] A. Furlenmeier, R. Lucas, H. B. MacPhillamy, J. M. Müller, and E. Schlittler, Exper. *9*, 331 (1953).

[3] Ciba's trade name for reserpine is "Serpasil".

[4] J. M. Müller, E. Schlittler, and H. J. Bein, Exper. *8*, 338 (1952).

[5] E. Späth and H. Bretschneider, Ber. dtsch. chem. Ges. *63*, 2997 (1930). – M. M. Janot, R. Goutarel, and R. Sneeden, Helv. chim. Acta *34*, 1205 (1951).

[1] K. Warnat, Helv. chim. Acta *14*, 997 (1931). – J. Calandra and J. Svarz, J. Amer. Chem. Soc. *72*, 1027 (1950).

[2] D. G. Harvey, E. J. Miller, and W. Robson, J. Chem. Soc. *1941*, 153.

[3] We are indebted to Drs. F. Bader and J. Müller of Ciba, Basle, for this information.

[4] J. Yost, Helv. chim. Acta *32*, 1297 (1949).

[5] Numbering according to Barger-Scholz, Helv. chim. Acta *16*, 1343 (1933).

Note added in proof: From the products of selenium dehydrogenation of reserpic acid methylester yobyrine and a substance $C_{19}H_{16}N_2O$ (Mp. 266°), probably 7-hydroxy-yobyrine, were isolated, affording more evidence for the presence in reserpine of the yohimbane skeleton. Compare communication to J. Amer. Chem. Soc. by A. F. St. André *et al.* and R. Schwyzer.