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 ± 17) rather than a 3α-configuration (standard value + 83 ± 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.

[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).

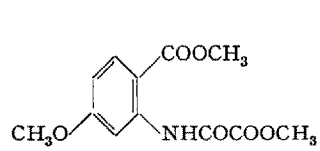
On the Constitution of Reserpine from *Rauwolfia serpentina* Benth[1]

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-oxalylanthranilic 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.



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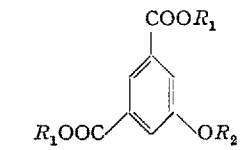


II: $R_1 = R_2 = CH_3$
III: $R_1 = H$; $R_2 = C_2H_5$

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].

[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).

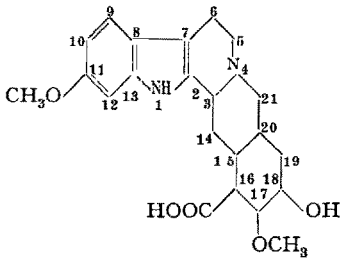
[2] D. G. HARVEY, E. J. MILLER, and W. ROBSON, J. Chem. Soc. *1941*, 153.

[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.



Details of our experimental work will be published elsewhere.

L. DORFMAN, C. F. HUEBNER, H. B. MACPHILLAMY, E. SCHLITTLER, and A. F. ST.ANDRÉ

Research Laboratories of Ciba Pharmaceutical Products, Inc., Summit, New Jersey, July 24, 1953.

Zusammenfassung

Bei der Permanganatoxydation und der Kalischmelze der Reserpinsäure wurden 4-Methoxy-oxalylanthranilsäure und 5-Oxyisophtalsäure isoliert. Als Arbeitshypothese wird deshalb für Reserpinsäure eine Yohimbanstruktur postuliert. Durch die obigen Abbauergebnisse ist die Stellung der einen Methoxylgruppe festgelegt, wogegen die Haftstellen der drei weiteren funktionellen Gruppen noch nicht gesichert sind.

A Note on Geissospermine

Some time ago we had the opportunity to investigate a limited amount of geissospermine. As our results do not quite agree with those reported in the literature, and as we do not anticipate a possibility to carry on this work, we report briefly our main findings. We have isolated geissospermine by the method of BERTHO and MOOG[1]. However, the amorphous product obtained this way failed to crystallize and was purified by chromatography on alumina. Geissospermine was eluted by ether-chloroform 1:1 and all the fractions crystallized easily from alcohol. After 8 crystallizations from ethyl acetate geissospermine melted at 217–219°. This compound is not a sesquihydrate as reported by BERTHO[2] (reported m.p. 210–212°) but is anhydrous. Found: C, 75·54%; H, 7·75%; N, 8·85%; N–CH_3, 1·17%; OCH_3, 4·72%; act. H, 0·17%; microhydrogenation uptake H_2, 0·78 moles. Titration in methyl-cellosolve gave one step with a pK of 7·18. Calculated for $C_{40}H_{50}O_3N_4$: C, 75·67%; H, 7·94%; N, 8·82%; N–CH_3, 2·36%; OCH_3, 4·88%. The I.R. spectrum of geissospermine has bands at 3580 and 3410 cm^{-1} belonging to OH or NH groups and in the carbonyl region a strong band at 1736 cm^{-1}. Otherwise the spectrum is too complex for assignments to be made at this stage. Cleavage of geissospermine with cold hydrochloric acid: Pure geissospermine (3·75 g) was ground with 10 ml of concentrated hydrochloric acid until no red color was produced with nitric acid as described by BERTHO[3]. The solution was poured on ice, made alkaline, and extracted with chloroform. The product (3·17 g) was purified by chromatography on alumina. The bulk of the product was eluted with 0·5% methanol in chloroform. The chromatographed base (1·04 g) was then subjected to a 50 funnel countercurrent distribution between chloroform and phosphate buffer pH 6·6. Besides smaller amounts of impurities and about 200 mg in the first funnels about 660 mg formed a homogeneous peak between the funnels 35 and 46. These were converted into a picrolonate and recrystallized to a constant m.p. of 238–240°C. Found: C, 61·64%, 61·94%; H, 6·20%, 5·99%; N, 14·66%. Calculated for $C_{19}H_{26}ON_2 \cdot C_{10}H_8O_5N_4$: C, 61·91%; H, 6·09%; N, 14·94%. The free base was liberated from the picrolonate and sublimed in high vacuum at 140° for analysis. Found: C, 76·25%; H, 8·77%; N, 9·35%; N–CH_3, 2·84%; OCH_3, 0·0%; act. H, 0·67%. Calculated for $C_{19}H_{26}ON$: C, 76·47%; H, 8·78%; N, 9·39%, N–CH_3, 5·04%. It is, therefore, clear that we have in our hands the N–CH_3 carrying moiety of geissospermine but that it does not in its pure form agree with the compound described previously by BERTHO[1]. The U.V. absorbtion of the compound is a typical dihydroindolic spectrum and it is of interest that the U.V. spectrum of geissospermine can be obtained by superimposing this spectrum on an indolic spectrum, for instance, that of cinchonamine. The I.R. spectrum of the $C_{19}H_{26}ON$ base shows a weak band at 3319 cm^{-1} and the carbonyl band at 1736 cm^{-1} is not present. Reduction of geissospermine with $LiAlH_4$ gave surprisingly a beautifully crystalline compound, m.p. 178–180°C. which was recrystallized from ethyl acetate. Found: C, 75·31%; H, 8·40%; N, 8·90%; OCH_3, 3·38%; N–CH_3, 1·68%, pK (methyl cellosolve) 8·00. Calculated for $C_{40}H_{52}N_4O_3$: C, 75·44%; H, 8·23%; N, 8·79%; OCH_3, 4·87%; N–CH_3, 2·36%. The U.V. absorbtion of the compound is similar to that of geissospermine. It is remarkable that in the I.R. spectrum of this dihydrogeissospermine the strong band at 1736 cm^{-1} remains unchanged. A strong band at 3150 cm^{-1} is much more prominent than the bands in this region in geissospermine. Another property by which dihydrogeissospermine differs strongly from geissospermine is the resistance to even warm concentrated hydrochloric acid by which geissospermine is immediately cleaved.

K. WIESNER, W. RIDEOUT, and J. A. MANSON

The Chemistry Laboratories, University of New Brunswick, Fredericton, New Brunswick, Canada, July 6, 1953.

Zusammenfassung

Die infraroten und ultravioletten Spektren und analytische Daten von Geissospermin wurden diskutiert. Die Spaltung von Geissospermin mit konzentrierter Salzsäure wurde wiederholt, und ein Spaltprodukt $C_{19}H_{26}ON_2$ wurde durch Gegenstromverteilung rein isoliert und durch ein kristallines Pikrolonat charakterisiert. Dieses Produkt besitzt ein Dihydroindolspektrum und trägt die N-methylgruppe des Geissospermins.

[1] A. BERTHO and F. MOOG, Ann. Chem. *509*, 241 (1934).

[2] A. BERTHO and G. VON SCHUCKMANN, Ber. dtsch. chem. Ges. *64*, 2278 (1931).

[3] A. BERTHO and H. F. SARX, Ann. Chem. *556*, 22 (1944).

[1] A. BERTHO and H. F. SARX, Ann. Chem. *556*, 22 (1944).