amount (36%) that it must have come in large part from the tetrahydro-10-isopropylbenzanthracene present, and in any case the elimination of the *meso*-isopropyl group in the course of the reaction is indicated. An analogous case is reported by Cook,[8] who observed the loss of an isopropyl group from the 5-position in the course of a selenium dehydrogenation.

Summary

Continuation of the high pressure hydrogenation of 2-(α-naphthoyl)-benzoic acid beyond the stage of reduction of the carbonyl group results in the fixation of hydrogen to the unsubstituted ring of the naphthalene nucleus. The structure of the resulting 2-(α-tetralylmethyl)-benzoic acid was established by synthesis. This acid is recognized as the precursor of a tetrahydro-10-isopropyl-1,2-benzanthracene previously isolated and now identified by synthesis as the 1′,2′,3′,4′-tetrahydro compound.

Supposed dihydro derivatives of 2-(α-naphthoyl)-benzoic acid and of 2-(α-naphthylmethyl)-benzoic acid have been identified as tetrahydro compounds, and the *ang.*-tetralanthraquinone of the literature has been shown to be impure.

CONVERSE MEMORIAL LABORATORY
CAMBRIDGE, MASSACHUSETTS

RECEIVED SEPTEMBER 20, 1937

(8) Cook, *J. Chem. Soc.*, 1592 (1933).

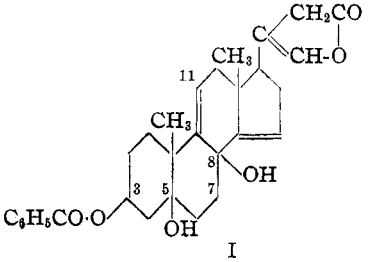
[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF HARVARD UNIVERSITY]

Convallatoxin

BY LOUIS F. FIESER AND ROBERT P. JACOBSEN[1]

Convallatoxin, the cardiac glycoside isolated by W. Karrer[2] from lily of the valley blossoms, is of particular interest because it surpasses all other known heart poisons in potency.[3] Tschesche and Haupt[4] established for the crystalline glycoside the formula $C_{29}H_{42}O_{10}$ and determined that the sugar component is a methyl pentose very probably identical with *l*-rhamnose. In contrast to the heart poisons which contain 2-desoxy sugars, convallatoxin belongs to the class in which the glycosidic linkage is highly resistant to hydrolysis. After prolonged boiling with aqueous-alcoholic sulfuric acid, Tschesche and Haupt succeeded in eliminating the sugar residue, but the reaction product, isolated as the benzoate, proved to be the monoanhydro derivative of the genin. In the Zerewitinoff test this benzoate liberated two moles of gas, which Tschesche and Haupt took as an indication of the presence of two free tertiary hydroxyl groups. Convallatoxin was found to give the Legal test and to be isomerized by alkali, indicating, respectively, that the glycoside probably contains the unsaturated lactone ring characteristic of the more common plant heart poisons and that a hydroxyl group is present at C_{14} to participate in the isomerization as well as in the establishment of an anhydro linkage during hydrolysis. From the observation that the glycoside absorbs one mole of hydrogen rapidly and a second mole very slowly, Tschesche and Haupt concluded that it contains an inert nuclear double bond in addition to the more active center of unsaturation in the lactone ring. Since anhydroconvallatoxigenin benzoate shows no selective absorption in the ultraviolet, the inert linkage evidently is not conjugated with the anhydro linkage.

From these observations, and on the assumption of the skeletal structure common to the other C_{23}-cardiac aglycones, Tschesche and Haupt suggested for anhydroconvallatoxigenin benzoate the formula I. The location of the nuclear double bond at a bridge head probably would account for its inert character, and the arrangement suggested for the tertiary hydroxyl groups was considered to be consistent with the persistence of these groups during treatment with acid. In a subsequent discussion of the problem, the objection was raised by one of us and Newman[5] that the tertiary hydroxyl group at C_8 would be subject to such



I

(1) Du Pont Research Fellow.

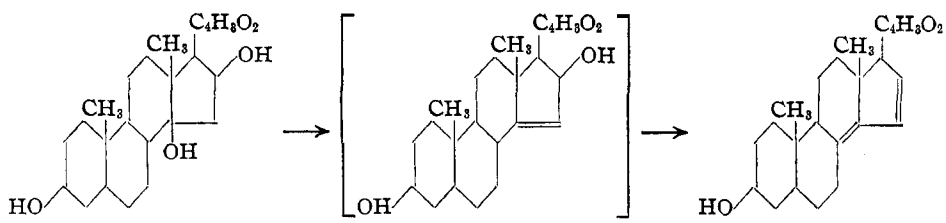
(2) W. Karrer, *Helv. Chim. Acta*, **12**, 506 (1929).

(3) K. K. Chen, A. L. Chen and R. C. Anderson, *J. Am. Pharm. Assoc.*, **25**, 579 (1936).

(4) Tschesche and Haupt, *Ber.*, **69**, 459 (1936).

(5) Fieser and Newman, *J. Biol. Chem.*, **114**, 707 (1936).

activation by the adjacent double bonds at the 9,11- and 14,15-positions that it would be expected to suffer ready elimination during the hydrolysis, with the establishment of a triene system conjugated in two directions. There is ample evidence to show that ease of dehydration, with the formation or extension of a conjugated system, is a property characteristic of α,β-unsaturated alcohols, even when the hydroxyl group is present in secondary combination.[6] Both allocholesterol and *epi*-allocholesterol are dehydrated rapidly by the action of hot, dilute hydrochloric acid;[7] although gitoxigenin contains but one tertiary hydroxyl group, it is converted by cold concentrated hydrochloric acid into a dianhydro compound.[8] It has been suggested[6] that the latter reaction probably involves the formation of a monoanhydro compound and the 1,4-elimination of water.



As an alternate proposal, Fieser and Newman suggested transposing the C_8-hydroxyl group of formula I to the angular methyl group at C_{10}, it being assumed that a primary hydroxyl in this hindered position would escape benzoylation. This assumption was soon recognized to be unjustified[9] since Jacobs and Elderfield[10] found that in the strophanthidin series the C_{10}-CH_2OH group can be benzoylated without difficulty. If two hydroxyl groups are present they must both, therefore, be tertiary. The recognition that there is no way of distributing two such groups in such a manner that they will be free from the activating influence of either the anhydro linkage or the inert nuclear double bond, suggested a reinterpretation[9] of the experimental results of Tschesche and Haupt. Of the two moles of gas liberated in the Zerewitinoff test, one may well come from the interaction of the reagent not with a hydroxyl group but with the active hydrogen atom of the lactone ring. Such a reaction has been observed by Jacobs[11] in a number of cases, and the failure of anhydrouzarigenin benzoate[4] to react in this way appears anomalous. Therefore, from the available evidence, anhydroconvallatoxigenin benzoate may contain only one free hydroxyl group. A possible disposition of the remaining oxygen atom was suggested from a reconsideration of the hydrogenation experiments. The results indicate the presence of a center of unsaturation which can be hydrogenated only with difficulty and this property is known to be associated not only with the presence of a nuclear ethylenic linkage in certain positions but with an aldehydic group at C_{10}, for Jacobs[12] found the aldehydic group of dihydrostrophanthidin to be very resistant to hydrogenation. From these considerations it seemed probable that the revision required in formula I consists in the transposition of both the C_8-hydroxyl oxygen atom and the dehydro linkage from the nucleus to the angular methyl group. Positions other than C_3 and C_5 are available for the benzoyloxy group and the tertiary hydroxyl group, but in analogy with other cardiac substances these locations are preferred.

The structure suggested is that of anhydrostrophanthidin benzoate, for which Jacobs and Collins[13] report the melting point 287–289°, whereas the benzoate of the same composition isolated by Tschesche and Haupt melted at 279–281°. The divergence of these values is hardly sufficient to establish the non-identity of the compounds. To be sure, Tschesche and Haupt in trial experiments observed no reaction of either the benzoate or convallatoxin itself with ketone reagents, but in view of the highly hindered character of an aldehydic group at C_{10} these negative results are hardly conclusive. In the hope of settling the matter, we decided to make a direct comparison of members of the two series.

Since Tschesche and Haupt obtained the anhydroaglycone benzoate in yield of only 11.5%

(6) Fieser, "Natural Products Related to Phenanthrene," 2nd edition, Reinhold Publishing Corp., New York, 1937, pp. 175, 280–282, 298, 362.

(7) Schoenheimer and Evans, *J. Biol. Chem.*, **114**, 567 (1936).

(8) Windaus and Schwarte, *Ber.*, **58**, 1515 (1925).

(9) Fieser, ref. 6, pp. 416–417.

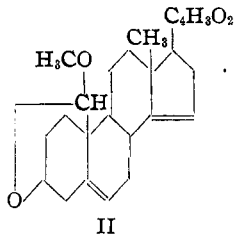
(10) Jacobs and Elderfield, *J. Biol. Chem.*, **113**, 611 (1936).

(11) Jacobs and Collins, *ibid.*, **65**, 491 (1925); Jacobs and Gustus, *ibid.*, **74**, 811 (1927); Jacobs and Elderfield, *ibid.*, **114**, 597 (1936).

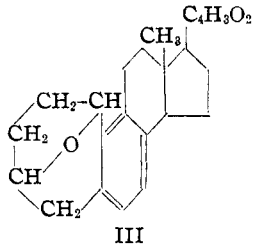
(12) Jacobs, *ibid.*, **88**, 519 (1930).

(13) Jacobs and Collins, *ibid.*, **59**, 713 (1924).

from the costly convallatoxin, we investigated as an alternate means of eliminating the sugar residue the method of alcoholysis recently applied successfully to convallamarin by Voss and Vogt.[14] This is based upon their observation that in simple cases alcoholysis of a glycosidic linkage proceeds much more rapidly than hydrolysis and is consequently less destructive to both the genin and the sugar, the latter being converted into the alkyl glycoside. After some trial, we found that by digesting convallatoxin with a dilute solution of hydrogen chloride in absolute methanol at 40° for ten days a crystalline, sugar-free reaction product could be isolated in fair yield (24%). Analysis of the compound indicated the formula $C_{24}H_{30}O_4$ which, in comparison with that of the unknown convallatoxigenin ($C_{29}H_{32}O_6$), points to an interaction of the liberated aglycone with methanol and the establishment of two anhydro linkages. The composition is that of the oxidodianhydrostrophanthidin methylal (II) described by Jacobs and Collins,[13] and indeed our compound corresponded



II

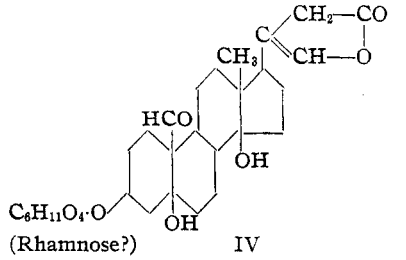


III

well with theirs in properties. Direct comparison with a sample of the methylal kindly supplied by Dr. W. A. Jacobs, as well as with a sample prepared from commercial strophanthin by the method of Jacobs and Collins,[13] established the identity of the substance obtained from convallatoxin. For further comparison, we applied to our alcoholysis product the methods developed by Jacobs and Collins for the preparation of dianhydrostrophanthidin,[13] its acetate,[13] and trianhydrostrophanthidin[15] (for which formula III has been suggested).[16] The three products were identical with authentic samples from strophanthidin.

This proof of the identity of the dianhydro derivatives of convallatoxigenin and strophanthidin leaves open the possibility that the genins differ in the steric arrangement at C_5 or C_{14}, for these asymmetric centers are destroyed in the establishment of the two anhydro linkages. Fortunately information is available on these points. While our work was in progress, Dr. R. Tschesche kindly informed us of his intention of testing the hypothesis advanced in the second edition of the senior author's book[9] by comparing the benzoate isolated by Tschesche and Haupt with that of anhydrostrophanthidin. We had at the time established the correspondence between dianhydro compounds of the two series, but before Dr. Tschesche had received our letter informing him of these results he had independently arrived at the same conclusion regarding the monoanhydro compounds. Following his generous suggestion that we include in our paper a statement of his observations, we may quote from his letter of July 30, 1937: "Inzwischen hatte ich auch hier festgestellt, dass Ihre Annahme richtig ist, dass das Benzoat des Anhydroconvallatoxigenins und das Benzoat des Anhydrostrophanthidins identisch sind. Sie stimmen im Schmelzpunkt, Mischschmelzpunkt und Drehung vollkommen überein." This observation clearly eliminates the possibility of an isomerism at C_5, and a difference between the two genins in the steric arrangement of the hydroxyl group at C_{14} is excluded by an earlier observation of Tschesche and Haupt. They found that convallatoxin, like other glycosides of the group, can be isomerized by alkali, yielding two iso compounds which probably differ only in the configuration at the new asymmetric carbon atom at C_{20}. If the C_{14} hydroxyl group of convallatoxin does not have the same steric arrangement as that of strophanthidin it is difficult to see how it can interact with the unsaturated lactone ring, for the steric arrangement at the point of attachment of this ring is clearly the same in each case. The aglycones convallatoxigenin and strophanthidin therefore are identical in every respect.

Assuming that the sugar residue is attached as



(Rhamnose?) IV

usual to the secondary hydroxyl group at C_3, convallatoxin can be assigned the structure IV,

(14) Voss and Vogt, *Ber.*, **69**, 2333 (1936).
(15) Jacobs and Collins, *J. Biol. Chem.*, **63**, 123 (1925).
(16) Fieser, ref. 6, pp. 274–275.

and it differs from the other glycosides of strophanthidin, cymarin and *k*-strophanthin-β, only in the nature of the sugar residue. Cymarin is strophanthidincymaroside, while in *k*-strophanthin-β a cymarose unit linked to the genin nucleus is combined in addition with a glucose unit; in each case the linkage to a 2-desoxy sugar renders the glycosidic linkage susceptible to ready hydrolysis. There is little difference in the cardiac activity of these two glycosides, and indeed the early information indicated that the nature of the sugar residue is of relatively little importance in determining the potency of the glycosidic heart poisons in general. It is, therefore, surprising that convallatoxin possesses considerably greater physiological activity than cymarin, the cat and frog units being reported[3] as 0.08 mg. per kg. and 0.00021 mg. per g. for the rhamnoside and 0.13 mg. per kg. and 0.00060 mg. per g. for the cymaroside; the more active glycoside is the one characterized by its resistance to hydrolysis. There are, however, other recent indications that the sugar residue can play a role of importance. Although the isomers α- and β-antiarin differ only in the structure of the sugar unit,[17] they display definite, if slight, differences in activity.[3] Neumann[18] has reported that the activity of the gitoxigenin glycosides varies considerably with the number and nature of the sugar residues.

We are indebted to the du Pont Company both for a fellowship award and for a grant for the purchase of a supply of convallatoxin.

Experimental Part[19]

Alcoholysis of Convallatoxin.—A suspension of 2 g. of commercial convallatoxin (colorless needles, m. p. 228–232°) in 30 cc. of absolute methanol containing 2.5% hydrogen chloride was allowed to stand in a glass-stoppered flask at 40° for ten days, with the addition on the fifth and eighth day of 5 cc. of 5% methyl alcoholic hydrogen chloride. The mixture acquired a brown color and became homogeneous after four or five days. At the end of the reaction period the solution was warmed gently on the steam-bath for fifteen minutes and cooled. After standing for some time at 4°, 340 mg. of solid material separated in the form of dark colored needles. After two crystallizations from methanol–acetone, using Norite, and one crystallization from ether–hexane, the product was obtained in the form of lustrous, colorless needles. After drying at 100° and 20 mm. over phosphorus pentoxide, the substance when introduced to a bath preheated to 230° melted at 251–254°, with preliminary sintering at 243°. The compound is moderately soluble in acetone, very slightly so in methanol or ether, and insoluble in hexane.

Anal. Calcd. for $C_{24}H_{30}O_4$: C, 75.36; H, 7.91. Found: C, 75.58; H, 7.68.

The substance did not depress the melting point of a sample of oxidodianhydrostrophanthidin methylal (II) obtained from Dr. W. A. Jacobs or of a sample of the methylal, m. p. 251–254°, which we prepared from strophanthidin according to Jacobs and Collins.[13] The substances also correspond in rotation in chloroform solution, that from convallatoxin giving the value $[\alpha]^{29}D$ −135° ($C = 0.333$), as compared with $[\alpha]^{24}D$ −131° ($C = 5.002$), reported by Jacobs and Collins.

Dianhydrostrophanthidin.—The crude product (340 mg.) resulting from the alcoholysis of convallatoxin was boiled under reflux for forty-five minutes with 40 cc. of 50% aqueous methanol containing 2% of hydrogen chloride, and the nearly homogeneous reaction mixture was diluted immediately with an equal volume of water and chilled. The crystalline solid which separated was dissolved, without being dried, in 20 cc. of 50% aqueous ethyl alcohol containing 2% of hydrogen chloride, and the solution was boiled for twenty minutes, diluted with an equal volume of water, and cooled. There was obtained 250 mg. of nearly colorless, crystalline solid, and one crystallization from methanol gave colorless needles. After thorough drying in vacuum, this melted, when introduced to a bath at 220°, at 231–235°, with previous sintering at 226°.

Anal. Calcd. for $C_{23}H_{28}O_4$: C, 74.97; H, 7.66. Found: C, 75.07; H, 7.78.

Mixed with authentic dianhydrostrophanthidin, m. p. 232–235°, prepared as described,[13] or with a sample kindly supplied for the purpose by Dr. W. A. Jacobs, the substance showed no depression in melting point.

The acetate, prepared from our material with the use of acetic anhydride and potassium acetate and crystallized from methanol, formed lustrous, flat needles melting at 203–208° (sintering at 199°) and did not depress the melting point of authentic dianhydrostrophanthidin acetate,[13] for which we found the m. p. 203–208° (J. and C., 203–206°).

Trianhydrostrophanthidin.—One hundred mg. of the hydrolysis product (m. p. 231–235°) was dissolved at room temperature in 2 cc. of concentrated hydrochloric acid with constant shaking. The mixture, at first bright yellow, soon became greenish yellow and turbid, and after one-half hour 20 cc. of cold water was added. The precipitated, chalky solid was washed with water, dried in vacuum at room temperature, and crystallized twice from ether–hexane, giving 25 mg. of lustrous, flat needles melting at 135.5–136.5°.

Anal. Calcd. for $C_{23}H_{26}O_3$: C, 78.82; H, 7.48. Found: C, 78.55; H, 7.58.

Authentic trianhydrostrophanthidin,[15] prepared in the same way, melted at 135.5–136.5° (J. and C. give 135.5–137.5 and 136–137°) either alone or mixed with the above sample.

(17) Tschesche and Haupt, *Ber.*, **69**, 1377 (1936).

(18) Neumann, *ibid.*, **70**, 1547 (1937).

(19) All melting points are corrected Analyses by Mrs. Verna R. Keevil.

Summary

From an analysis and reinterpretation of the results of Tschesche and Haupt it was concluded that the formula for convallatoxin tentatively suggested by these investigators is inadmissible and that the (unisolated) aglycone in question probably is identical with strophanthidin. Comparisons made both in this Laboratory and by Dr. Tschesche have now established the correctness of this hypothesis.

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CAMBRIDGE, MASSACHUSETTS

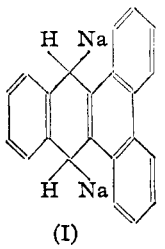
RECEIVED SEPTEMBER 23, 1937

[CONTRIBUTION FROM THE CHEMISTRY LABORATORY OF THE UNIVERSITY OF MICHIGAN]

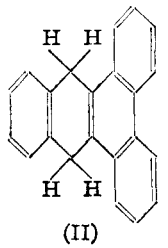
The Reaction of Alkali Metals with Polycyclic Hydrocarbons. II

BY W. E. BACHMANN AND L. H. PENCE[1]

It was shown recently that sodium and lithium add to the *meso* positions of 1,2-benzanthracene, 1,2,5,6-dibenzanthracene and 3-methylcholanthrene.[2] We have now extended this reaction to include 5-methyl-1,2-benzanthracene, 5-phenyl-1,2-benzanthracene, 1,2,3,4-dibenzanthracene, 6-methyl-1,2,3,4-dibenzanthracene, 1,2,6,7-dibenzanthracene and 1,2,3,4,5,6-tribenzanthracene. Intensely colored addition compounds are formed when solutions of these hydrocarbons in ether–benzene are shaken with sodium or with lithium. Thus, 1,2,3,4-dibenzanthracene gives an intensely lavender colored solution of 9,10-disodium-9,10-dihydro-1,2,3,4-dibenzanthracene (I), while with lithium the intensely purple 9,10-dilithium addition product is formed.



(I)

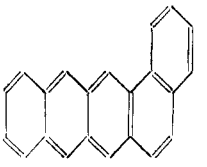


(II)

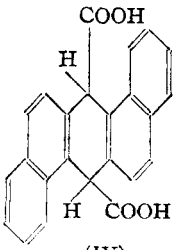
As a rule the color of the disodium addition product is different from that of the dilithium derivative. This difference is ascribed to a difference in the mode of addition of the two metals, the one adding in *cis* positions, the other in *trans* positions. On treatment with methanol, the alkali addition products of the hydrocarbons yield the 9,10-dihydro derivatives (II, for example). The same dihydro derivative is obtained from both the disodium and the dilithium addition compounds, except in the case of 1,2,6,7-dibenzanthracene (III). In the reaction between the alkali metals and 1,2,6,7-dibenzanthracene it was expected that addition could take place at the 5,8- or the 9,10-positions. Actually, a mixture of the two possible dihydro derivatives was obtained from the sodium addition product and methanol. A single dihydro compound was isolated from the dilithium addition product, although the structure of this compound was not determined.

The structures assigned to the dihydro derivatives and hence to the alkali metal addition products are based on the oxidation of the dihydro derivatives to the 9,10-diones by chromic acid. All of the 9,10-dihydro derivatives are dehydrogenated readily by sulfur to the parent hydrocarbons.

In order to obtain water-soluble derivatives of the polycyclic hydrocarbons, we have investigated the action of carbon dioxide on a number of the



(III)



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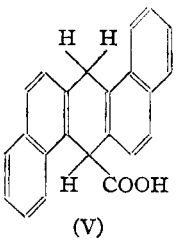

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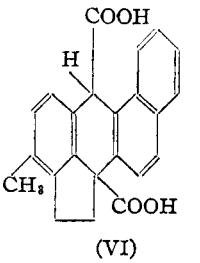

(VI)

alkali addition products. In this reaction a distinct difference in behavior was encountered

(1) From the Ph.D. dissertation of L. H. Pence.
(2) Bachmann, *J. Org. Chem.*, **1**, 347 (1936).