the design of the pressure regulator[13] which permitted the gas to enter the evacuated chamber while the combustion was carried out at atmospheric pressure. The mercury valve allowed the passage of gas through the fritted disc when the pressure in the combustion flask rose above a value determined by the setting of the side-arm.

Radioactivity Determinations.—A dynamic condenser electrometer was used to determine the ionization current, the measured quantity being the voltage drop across a known high-valued resistor (10^{11} ohms). To convert current readings to disintegrations per second, the factor 1×10^{-16} ampere per disintegration per second was used, and these values were then converted to millicuries by the factor 3.7×10^{7} disintegrations per second per millicurie.

The background current was determined prior to each filling of the chamber. It was found to remain practically constant at 5×10^{-16} ampere, *i. e.*, negligibly small in comparison with the activities being determined.

In our procedure, a complete assay required about one hour, of which about fifteen minutes were taken in determining the background current, thirty minutes in weighing the sample and carrying out the combustion, and ten minutes in measuring the activity. The error in the analyses is estimated to be about 1%.

Summary

Mandelic acid, labelled C^{14} in the α-position, was obtained from similarly labelled phenylglyoxal on treatment with alkali, thus demonstrating that no rearrangement of the carbon skeleton occurs and consequently that the reaction proceeds by a shift of the aldehydic hydrogen atom. The similar reaction of α,α-dibromoacetophenone with aqueous alkali has also been shown to occur without rearrangement.

RECEIVED JUNE 1, 1948

(13) This device was designed by Dr. W. B. Leslie, present address: Clovis, New Mexico.

[CONTRIBUTION FROM THE LABORATORIES "SYNTEX," S. A.]

Steroidal Sapogenins. I. Transformation of Kryptogenin into Diosgenin and Pseudodiosgenin

BY ST. KAUFMANN AND G. ROSENKRANZ

In the course of the past two years we have carried out in our Laboratories intensive studies on various steroidal sapogenins which appeared to us to be potential raw materials suitable for the manufacture of steroidal hormones. At that time, of all the known steroidal sapogenins, only diosgenin and its steroisomer, yamogenin, were of importance in the industrial preparation of hormones. In 1943, Marker, *et al.*,[1] described a new sapogenin, kryptogenin (I), isolated from the sapogenin fraction of extracts of Beth root. As this sapogenin occurs in important quantities in several species of Mexican dioscoreae as a constant companion of diosgenin and yamogenin, it was obvious to us that this natural product represented an important potential raw material and our efforts were concentrated on the transformation of this substance into other sapogenins or their derivatives suitable for the production of hormones.

Recently, Marker, *et al.*,[2] reported the reduction of kryptogenin by sodium and isopropyl alcohol and also by aluminum isopropylate and the subsequent isolation of diosgenin from the reduction mixture. On reproducing these reactions we found that only very small amounts of diosgenin are formed. In the course of the reduction of kryptogenin with sodium and alcohol the main reaction, as was to be expected, consisted in self-condensation of kryptogenin to fesogenin and subsequent reduction of this condensation product. In fact, we obtained fesogenin in good yield by refluxing kryptogenin with sodium alcoholate in alcoholic solution, in agreement with the observation of Marker, *et al.*,[3] who obtained fesogenin by the reaction of kryptogenin diacetate with alcoholic potassium hydroxide.

In order to establish the exact reduction conditions and to improve the yields of diosgenin, we submitted kryptogenin and its diacetate to catalytical hydrogenation using Raney nickel as catalyst in neutral medium. Marker, *et al.*, already have described the catalytical reduction of kryptogenin in acidic medium and in presence of platinum oxide as catalyst. By varying the conditions they obtained as main product 5,6-dihydrokryptogenin, tigogenin or dihydrotigogenin,[4] respectively.

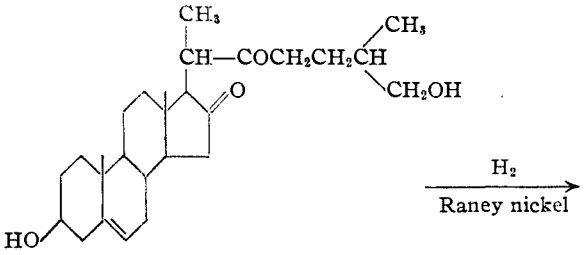
We found that in neutral medium and in presence of Raney nickel only the ketonic group in 16 is reduced and we were able to isolate the 16-dihydrokryptogenin in good yield. This compound is comparatively unstable and very reactive. It is dehydrated by mineral or strong organic acids to diosgenin (III) and by boiling acetic anhydride to diosgenin acetate. The diacetate of 16-dihydrokryptogenin obtained by the catalytical hydrogenation of kryptogenin diacetate in the presence of Raney nickel in neutral medium is a colorless oil and can be saponified in alkaline solution to 16-dihydrokryptogenin. On the other hand, 16-dihydrokryptogenin diacetate is readily converted to pseudodiosgenin diacetate (IV) by dehydrating agents, such as phosphorus oxychloride, thionyl chloride, etc. The 16-dihydrokryptogenin can theoretically exist in three tautomeric forms (IIa, IIb, IIc). The above reactions can be illustrated by the formulas

(1) Marker, Wagner, Goldsmith, Ulshafer and Ruof, THIS JOURNAL, **65**, 739 (1943).

(2) Marker, Wagner, Ulshafer, Wittbecker, Goldsmith and Ruof, *ibid.*, **69**, 2198 (1947).

(3) Ref. 2, p. 2201.

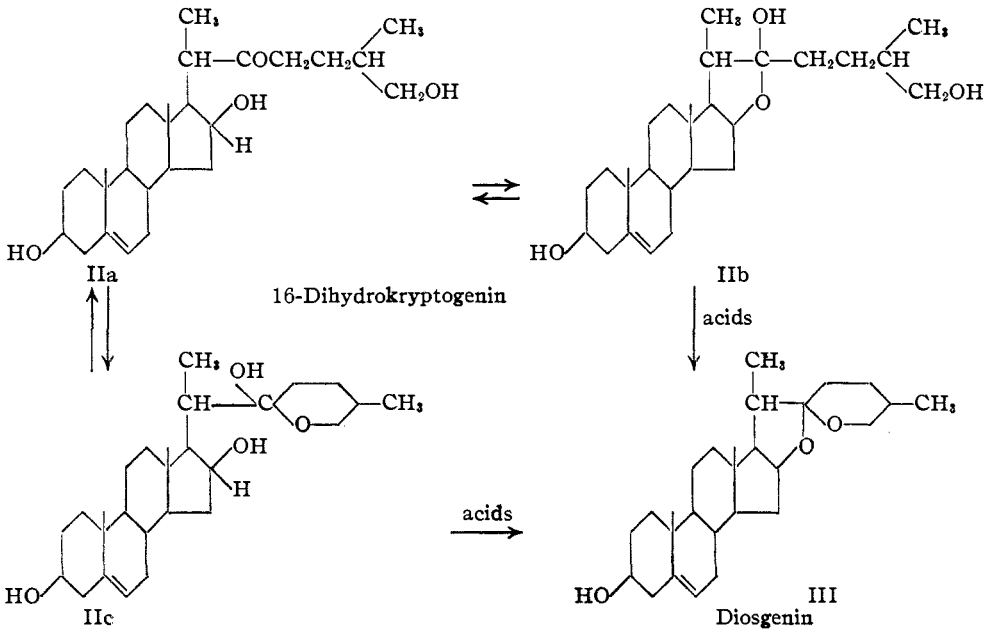
(4) Ref. 2, p. 2199.

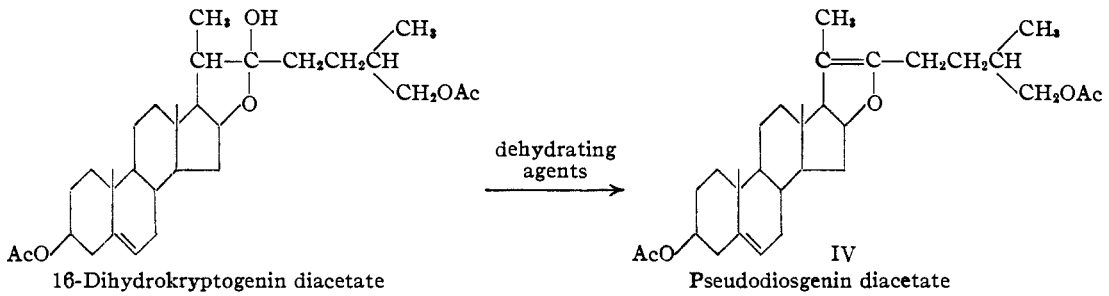


I
Kryptogenin

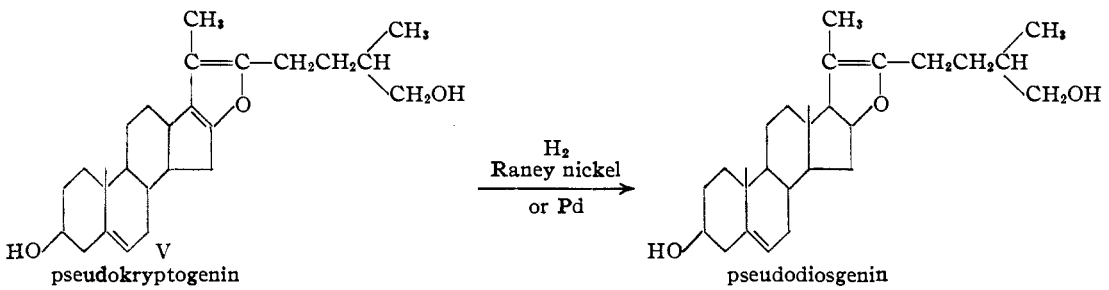
ditions only the 16-17 double bond is reduced forming pseudodiosgenin or its diacetate in almost quantitative yield. Marker, *et al.*[5] hydrogenated pseudokryptogenin in the presence of platinum oxide in acidic medium and obtained dihydropseudotigogenin.

By these reactions a practical conversion of kryptogenin into various steroidal hormone intermediates has been accomplished. Apart from this, the isolation and identification of the 16-dihydrokryptogenin, which easily can be trans-





We also submitted pseudokryptogenin (V) and its diacetate to catalytical hydrogenation in neutral medium containing Raney nickel or palladium–barium sulfate catalyst. Under these conformed into diosgenin, strongly supports Marker's hypothesis of the constitution of naturally occurring saponins. The existence of open side chain



(5) Ref. 2, p. 2209.

sapogenins with a hydroxyl group in the position 16 and a ketonic group in 22 or its tautomeric cyclic hemiketal has been postulated before by Marker, *et al.*,[6] as an explanation for the natural occurrence of steroidal saponins with many sugar groups. It is not impossible that our 16-dihydrokryptogenin is identical with the aglucon of the original saponins.

Experimental[7]

Reaction of Kryptogenin with Sodium Alcoholate.—Pure kryptogenin (10 g.) is dissolved in 200 cc. of absolute alcohol and a solution of sodium alcoholate obtained by dissolving 2 g. of sodium in 100 cc. of absolute alcohol is added. The mixture is refluxed for two hours on the water-bath, then precipitated in water. The precipitate is extracted with ether and the ether solution washed neutral with water. The ether extract is dried with anhydrous sodium sulfate and evaporated to dryness. The residue is crystallized from ethyl acetate–hexane, whereby 3 g. of pure fesogenin, m.p. 179–180°, is obtained. No unchanged kryptogenin could be recovered from the mother liquors. *Anal.* Calcd. for $C_{27}H_{40}O_5$: C, 78.64; H, 9.70. Found: C, 78.90; H, 9.81.

The diacetate[8] is prepared by acetylating fesogenin with acetic anhydride and pyridine. Recrystallized from methanol it melts at 134–135°. *Anal.* Calcd. for $C_{31}H_{44}O_5$: C, 75.00; H, 8.87. Found: C, 74.88; H, 9.00.

16-Dihydrokryptogenin.—Pure kryptogenin (60 g.) is dissolved in 600 cc. of pure alcohol and 30 g. of freshly prepared Raney nickel is added. The mixture is agitated under hydrogen pressure (45 lb.) for two hours. The nickel is filtered off and the filtrate evaporated to dryness. The colorless residue is crystallized from acetone. Thirty grams of 16-dihydrokryptogenin is obtained, m.p. 173–175°; $[\alpha]^{20}D$ −47° (in chloroform). *Anal.* Calcd. for $C_{27}H_{44}O_4$: C, 75.00; H, 10.18. Found: C, 75.16; H, 10.05.

A solution of 16-dihydrokryptogenin in alcohol is treated with a few drops of concentrated hydrochloric acid. After a few seconds pure diosgenin crystallizes in almost quantitative yield, m.p. 203–205°. Mixed with an authentic sample of diosgenin it gives no depression, $[\alpha]^{20}D$ −119° (in chloroform).

Acetate m.p. 195–196°; mixed with an authentic sample of diosgenin acetate it gives no depression, $[\alpha]^{20}D$ −118° (in chloroform).

Anal. Calcd. for $C_{29}H_{44}O_4$: C, 76.31; H, 9.65. Found: C, 76.14; H, 9.84.

An almost instantaneous transformation of 16-dihydrokryptogenin into diosgenin can be achieved by dissolving it in glacial acetic acid; after a few seconds diosgenin begins to crystallize. Boiling acetic anhydride transforms 16-dihydrokryptogenin immediately into diosgenin acetate. The identity of the substances was proved by microanalysis, melting point, mixed melting points and rotations.

16-Dihydrokryptogenin Diacetate.—Kryptogenin diacetate is hydrogenated in the manner described for the hydrogenation of kryptogenin. The reduction product is a colorless oil which could not be crystallized. By alkaline saponification 16-dihydrokryptogenin, m.p. 173–175°, $[\alpha]^{20}D$ −47° (in chloroform), is obtained. Mixed with a sample of 16-dihydrokryptogenin prepared as above described, no depression of the melting point could be observed.

Pseudodiosgenin Diacetate from 16-Dihydrokryptogenin Diacetate.—Fifty grams of 16-dihydrokryptogenin diacetate is dissolved in 200 cc. of dry pyridine and 20 cc. of phosphorus oxychloride added. The mixture is refluxed for three-quarters hour and poured into water and ice. The precipitate is extracted with ether, washed neutral and the ether solution dried and evaporated. The residue crystallizes from methanol (25 g.). The beautiful plates of pseudodiosgenin diacetate melt at 97–98°. Mixed with an authentic sample of pseudodiosgenin diacetate it gives no depression; $[\alpha]^{20}D$ −31° (in chloroform). *Anal.* Calcd. for $C_{31}H_{46}O_5$: C, 74.69; H, 9.23. Found: C, 74.99; H, 9.19.

Saponification of the diacetate with alcoholic potassium hydroxide yields pseudodiosgenin, m.p. 194–196°. Mixed with an authentic sample of pseudodiosgenin it gives no depression, $[\alpha]^{20}D$ −103° (in chloroform). *Anal.* Calcd. for $C_{27}H_{42}O_3$: C, 78.26; H, 10.14. Found: C, 78.30; H, 9.82.

16-Dihydrokryptogenin diacetate can also be transformed into pseudodiosgenin diacetate by other dehydrating agents, such as boiling acetic anhydride or tetralin.

Pseudodiosgenin from Pseudokryptogenin.—Pseudokryptogenin (10 g.) is dissolved in 500 cc. of pure alcohol and 5 g. of freshly prepared Raney nickel added. The mixture is agitated in hydrogen atmosphere (45 lb.) for two hours. The catalyst is filtered off and the filtrate is evaporated to dryness. The residue is crystallized from alcohol; pure pseudodiosgenin is obtained in almost quantitative yield, m.p. 194–196°. *Anal.* Calcd. for $C_{27}H_{42}O_3$: C, 78.26; H, 10.14. Found: C, 78.29; H, 10.14. Acetate with boiling acetic anhydride, m.p. 97–98°, $[\alpha]^{20}D$ −31° (in chloroform).

For further identification the diacetate of pseudodiosgenin thus obtained was oxidized with chromic acid in glacial acetic acid by the method of Marker[9] and the acetate of Δ-5,16-pregnadien-ol-(3)-one-(20) was obtained in good yield,[10] m.p. 175–177°. *Anal.* Calcd. for $C_{23}H_{32}O_3$: C, 77.52; H, 8.98. Found: C, 77.62; H, 8.89.

Pseudodiosgenin also can be obtained by carrying out the hydrogenation of the pseudokryptogenin in ethyl acetate and utilizing palladium–barium sulfate catalyst.

Pseudodiosgenin Diacetate from Pseudokryptogenin Diacetate.—The pseudokryptogenin diacetate was prepared by acetylating pseudokryptogenin with boiling acetic anhydride. The acetate crystallized in well-built prisms. We found the melting point after several recrystallizations to be 93–94° in contradiction to Marker, *et al.*, who reported two melting points: 114 and 124°.[11] Our product, which has an optical rotation $[\alpha]^{20}D$ −35° (in alcohol), gave the correct analysis. *Anal.* Calcd. for $C_{31}H_{44}O_5$: C, 74.75; H, 8.89. Found: C, 74.86; H, 8.72.

Ten grams of pseudokryptogenin diacetate is dissolved in 100 cc. of alcohol and 5 g. of freshly prepared Raney nickel added. The mixture is agitated in hydrogen atmosphere (45 lb.) for two hours, the catalyst is filtered off and the filtrate is evaporated to dryness. The residue is crystallized from methanol in plates, m.p. 97–98°. Mixed with an authentic sample of pseudodiosgenin diacetate it gives no depression. The same product is obtained by dissolving the pseudokryptogenin diacetate in ethyl acetate and utilizing palladium–barium sulfate catalyst.

Summary

1. Kryptogenin and its diacetate have been reduced with Raney nickel to 16-dihydrokryptogenin and its diacetate, respectively.

2. Strong evidence has been presented that the 16-keto group of kryptogenin is more reactive than the 22-keto group.

3. 16-Dihydrokryptogenin has been converted to diosgenin and diosgenin acetate.

4. 16-Dihydrokryptogenin diacetate has been

(6) R. E. Marker and Josefina López, *ibid.*, **69**, 2389 (1947).

(7) Microanalysis by Dra. L. Norymberska of the Instituto Politécnico Nacional, México, D. F., and Dr. Carl Tiedcke, New York, N. Y.

(8) This diacetate has not been reported in crystalline form before.

(9) R. E. Marker, THIS JOURNAL, **62**, 3351 (1940); R. E. Marker and Josefina López, *ibid.* **69**, 2383 (1947).

(10) Butenandt, *Ber.*, **72**, 182 (1939); Goldberg, *Helv. Chim. Acta*, **20**, 1186 (1940).

(11) Ref. 2, p. 2208.

transformed to pseudodiosgenin diacetate.

5. Pseudokryptogenin and its diacetate have been reduced catalytically to pseudodiosgenin and its diacetate, respectively.

6. Three practical methods for the transformation of kryptogenin into steroidal hormone intermediates have been described.

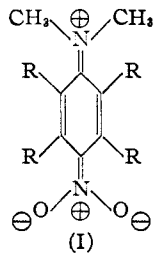
MEXICO, D. F. RECEIVED APRIL 15, 1948

[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY OF THE UNIVERSITY OF MINNESOTA]

Steric Effect of Methylene Groups. IV

BY RICHARD T. ARNOLD AND JOHN RICHTER[1]

By making use of a large variety of physical and chemical methods,[2] it has been clearly demonstrated that resonance in aromatic nitro compounds is hindered by ortho substituents R which inhibit coplanarity of the benzenoid ring and the electron-donor (*i. e.*, $(CH_3)_2N$–) or electron-acceptor (*i. e.*, $-NO_2$) groups.

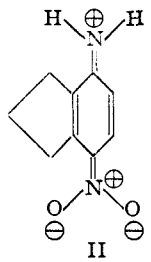


(I)

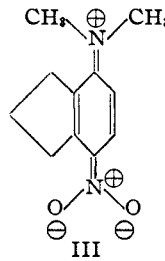
p-Nitro-N,N-dimethylaniline (I, R = H) is essentially a flat molecule due to the contribution of the quinoidal structure to the resonance. As the group R increases in size, there is an increasing repulsion between R and the amino[3] and nitro[4] groups. Remington[3] has shown that the marked ultraviolet absorption (near 380 mμ) of certain nitrobenzene derivatives is associated with the quinoidal limiting structure (I). The intensity of this band is steadily reduced as the group R increases in volume.

We have made use of this fact in a determination of the relative steric influence of methylene groups in five- and six-membered rings.

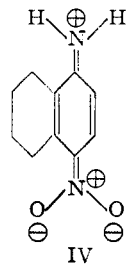
Compounds II–V (represented above in their quinoidal limiting structures) have been prepared



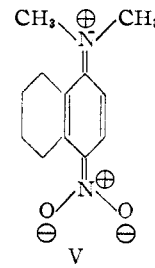
II



III



IV



V

and examined in the ultraviolet region. Table I includes a summary of the pertinent absorption maxima and intensities.

TABLE I[a]

	Compound	Max. (in mμ)	(Molar)
II	4-Amino-7-nitrohydrindene	376	13,900
	(*p*-Nitroaniline)	(374)	(15,700)
III	4-N,N-Dimethylamino-7-nitrohydrindene	387	12,600
	(N,N-Dimethyl-*p*-nitroaniline)	(386)	(18,290)[3]
IV	5-Amino-8-nitro-1,2,3,4-tetrahydronaphthalene	383	11,400
V	5-N,N-Dimethylamino-8-nitro-1,2,3,4-tetrahydronaphthalene	364	5,900

[a] Measurements were made in 95 per cent. ethanol using a Beckman spectrophotometer.

The free amino groups in II and IV are not appreciably affected by the ortho substituents.[3] Presumably the difference between II and IV can be attributed largely to a steric repulsion between the nitro and methylene groups.

When *p*-nitroaniline is converted into *p*-nitro-N,N-dimethylaniline a considerable increase is observed in the absorption band near 380 mμ. This is, perhaps, largely due to the electron repelling effects of the methyl groups which increase the basicity and facilitate electron release toward the nitro group as indicated in I. This effect is more than counterbalanced, however, when ortho substituents are present, and increases with the size of the substituent due to steric inhibition of the resonance.

Differences in the extinction coefficients of II and IV and the changes brought about when these two compounds are methylated to give III and V strongly support, we believe, the view that methylene groups in hydrindene provide a smaller steric

(1) This manuscript was written from the Ph.D. thesis of John Richter. Present address: Merck & Company, Rahway, New Jersey.

(2) G. W. Wheland, "The Theory of Resonance," John Wiley and Sons, Inc., New York, N. Y., 1944, p. 136.

(3) Remington, THIS JOURNAL, **67**, 1838 (1945).

(4) Brown and Reagan, *ibid.*, **69**, 1032 (1947).